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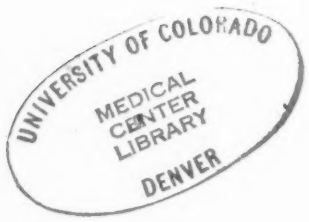

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CEREBELLAR ABSCESS

TREATMENT BY EXCISION WITH THE AID OF ANTIBIOTICS

BY

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(RECEIVED FOR PUBLICATION, NOVEMBER 20, 1947)

In a series of one hundred brain abscesses treated in the Nuffield Department of Surgery, Oxford, in the past nine years there were eighteen cerebellar abscesses. With one probable exception they were all due to mastoid infection, and were rather less frequent than temporal-lobe abscess due to the same cause, of which there were twenty-two cases. Of the first nine cases of cerebellar abscess, only two survived, whereas of the last nine, eight have recovered and it is this encouraging experience which we wish to record. The division of the material into two groups of nine cases each is significant because none of the first group was treated with penicillin, whereas all of the second group had the advantage of that preparation. Previous reports deal chiefly with single cases or small series emphasizing the gravity of cerebellar abscesses: thus Sachs (1946) reported eleven cases of which five recovered. Most neurosurgeons and otologists agree that these are among the most dangerous of intracranial abscesses.

During the whole of this period we have attempted to deal with brain abscesses in such a way that they could ultimately be excised. In the case of cerebral abscess this usually entailed repeated aspiration, sometimes combined with a decompression as advocated by Vincent and others (1937), the instillation of thorotrast for radiographic control (Kahn, 1939), and, latterly, instillation of penicillin into the abscess in an attempt to sterilize it. When it was reckoned that the abscess was sufficiently encapsulated to allow dissection, an osteoplastic flap was reflected, and the abscess was extirpated much as a solid tumour. These principles are now in common use and there is abundant evidence that they comprise an effective method of dealing with cerebral abscesses. But applying the same principles to the treatment of cerebellar abscesses we met with repeated disappointments, and, as noted, only two of the first nine cases recovered, one with decompression and repeated aspiration, and the other with decompression and aspiration followed by excision. The following cases demonstrate many of the problems involved.

Cases Treated without Penicillin

Case 1.—A 16-year-old girl was admitted on April 17, 1940, complaining of severe paroxysmal headache. She was said to have had a discharge from the right ear at the age of 4 years, ascribed to the retention of a piece of cotton wool in the ear. The discharge ceased when the wool was removed, but throughout her childhood she was prone to bilateral earache when she had a cold. Apart from this she was in good health until Feb. 18, 1940, when she complained of right-sided earache. This lasted for two or three days and subsided with local treatment, but a severe recurrence ten days later led to her admission to another hospital where a myringotomy was performed. Four days later, on March 8, a right-sided mastoid operation was done. The operation note described "a cellular infected mastoid. Lateral sinus and dura and middle fossa appeared to be normal."

For the first week after the mastoid operation she vomited frequently and complained of a good deal of headache. These symptoms subsided in the second week, and she started getting up and about. During the third week the headache and vomiting recurred, and a lumbar puncture on March 24 showed 20 lymphocytes and 50 mg. of protein in the cerebrospinal fluid. On this day some nystagmus was noted for the first time. The headache got steadily worse until on the day before admission she was screaming with it.

On examination on April 17, she was drowsy but could be roused to co-operate adequately. She complained of severe headache, and held her head rigidly bent forward and to the left, resenting any attempt to move it. There was a moderate slurring dysarthria, but no aphasia. The positive neurological abnormalities amounted to bilateral papillœdema (3 diopters), slow coarse nystagmus on looking to the right, rapid and finer nystagmus on looking to the left, and gross ataxy of the right arm and to a much less extent of the right leg. The right mastoid incision had healed with the exception of a small pellicle in the centre of the wound. These signs pointed clearly to an expanding lesion in the right cerebellar lobe and there seemed to be no reasonable doubt that it was an abscess.

On the following day, under general anæsthesia the posterior fossa was explored and a right cerebellar abscess aspirated. The mastoid scar was used as the right limb of an inverted U-shaped incision and the muscle was reflected from the right two-thirds of the posterior fossa. The exposed bone was removed, including the posterior margin of the foramen magnum. Through the unopened dura, an exploring needle encountered the wall of the abscess at a depth of 1 cm., and 20 c.cm. of pus were aspirated (from this pneumococcus type I was cultured), and 2 c.cm. of thorotrast was instilled. This slackened the dura considerably and the wound was closed without drainage.

There was immediate improvement. The headache was relieved, the patient became quite alert and cheerful, and the cerebellar signs were much less marked although still present. Radiographs showed the abscess outlined by thorotrast in the right cerebellar lobe (Fig. 1). The patient was given sulphonamides by mouth from the time of operation, and this treatment was continued until May 7.

Improvement was maintained until April 24 (six days after aspiration of the abscess), when she suddenly complained of severe headache which made her scream, the pulse rate increased from 70 to 140 per minute, her neck was very stiff, and she had a positive Kernig's sign. The cerebellar signs were more marked, but the general picture suggested meningitis, made more likely by the fact that a routine lumbar puncture two days earlier had shown that there were 1,800 cells per c.mm. in the spinal fluid although at that time there were no clinical signs of meningitis. A further *x*-ray examination, however, showed that there had been a considerable increase in the size of the abscess (Fig. 2), whereas a lumbar puncture showed that the fluid was now clear and there were only 20 cells per c.mm. It was thus clear that the recrudescence of symptoms was due to increase in size of the abscess rather than to meningitis. It was accordingly aspirated through a sharp needle, 20 c.cm. of pus being removed.

From this time there was steady improvement. The headache ceased, and the neurological abnormalities became much less marked. Radiographs taken at regular intervals showed that the abscess was steadily diminishing in size, until ultimately it became a small crenated mass (Fig. 3). The patient started getting up on May 7, and was discharged from hospital on May 28, 1940, at which time she was free from symptoms, the papillœdema had subsided, and no neurological abnormalities could be demonstrated. She has remained well, reporting last in July, 1947, that she was married and expecting a baby shortly.

COMMENT.—In this case, it was not necessary to remove the abscess, as from the clinical and radiological evidence it resolved after a bony decompression and two aspirations.

The next case is typical of the disappointments which were so common in the first group: three weeks after excision of a cerebellar abscess, the patient died from pneumococcal meningitis.

Case 2.—A girl aged 12 years was admitted on June 13, 1939, complaining of severe headache and vomiting. She had been in good health until three months before admission, when she had bilateral earache and some purulent discharge from the right ear for four days. The discharge eased the pain, and she seemed to be quite well until a fortnight later, that is, about ten weeks before admission, when she came home from school complaining of severe headache. At first it was generalized, but as time went on it seemed to settle chiefly in the back of the head and neck, and she vomited frequently. At times, there were paroxysms of headache which made her scream. For one week before admission she had been confined to bed: the headache seemed to be somewhat easier, but she became drowsy and apathetic and the vomiting continued. There had been no recurrence of the earache and aural discharge.

On admission to hospital she was conscious and co-operative, but during the first examination she vomited suddenly and complained of severe pain in the back of the neck. Her speech was punctuated by hiccoughs but there was no dysarthria or aphasia. The temperature was 98° F., pulse rate 110 per minute, respirations 24 per minute. She held her neck rigidly and resented any attempt to move it. Both ears were dry and there was no deafness, but she complained of some tenderness on pressure over the right suboccipital and mastoid regions.

The neurological abnormalities amounted to bilateral papillœdema (4 diopters), a slight right external rectus weakness, nystagmus which was slow and coarse on looking to the right and rapid and finer on looking to the left, slight right facial weakness, profound hypotonia, and ataxy and dysdiodokokinesis of the right limbs, the arm being more affected than the leg. Radiographs of the skull showed early separation of the sutures.

The clinical features suggested an expanding lesion in the right cerebellar lobe and the relation to aural infection made an abscess the most likely diagnosis. The patient was clearly on the brink of disaster and she was operated on ten hours after admission. Lumbar puncture immediately before operation showed the pressure to be 420 mm.; the fluid contained 40 mg. protein per 100 c.cm. and 15 white cells per c.mm., 80 per cent. of which were lymphocytes.

The operation was done under local anæsthesia. Both ventricles were tapped and were found to be capacious. An ordinary cerebellar exploration was then made. The foliæ of the right cerebellar lobe were broad and pale and an exploring cannula met resistance at a depth of 1 cm. This proved to be the capsule of the abscess, and it was so tough that it could not be pierced with a cannula but required a sharp needle, through which 10 c.cm. of thick yellow pus were aspirated. A circular area of cerebellar cortex (3 cm. in diameter) was excised to expose the capsule of the abscess, and traction sutures were inserted. The abscess was then dissected from the surrounding white matter, and no great difficulty was encountered until its site of attachment to the petrous bone was reached. It was then found that the tough capsule gave way to a layer of friable granulation tissue adherent to the petrous bone, and in scraping this free the abscess ruptured and some pus escaped into the field. The

abscess was then lifted out. The site of attachment was scraped clean and the obviously infected field treated with pledgets of wool soaked in azochloramide in tracetin. When these were removed and all bleeding points stopped the wound was closed in the usual manner without drainage. The pus from the abscess was sterile on culture and no organisms were seen in films.

There was some improvement for about forty-eight hours after operation, notably in relief of headache and vomiting, lessening of ataxy, and improvement of ocular movements. On the third post-operative day the patient had a good deal of discomfort in the wound, and it was found to be inflamed, especially at the right end of the incision ; two or three days later it began to discharge a little thin, serous pus from which pneumococcus was grown. The wound continued to discharge from that time, and in addition to the pneumococcus a staphylococcus aureus was often cultured.

She was given sulphonamides by mouth from the time of operation and parenterally from the fourth to the sixteenth day after operation. Daily lumbar punctures were done, and by the eighth post-operative day the fluid was clear and colourless and contained 20 mg. of protein per 100 c.cm. and 8 cells per c.mm. Thereafter, the protein and cell content increased slightly, until on the sixteenth post-operative day there were 110 mg. protein and 191 cells, 74 per cent. of which were polymorphs. No organisms had been seen in the cerebrospinal fluid, and cultures were sterile. Nevertheless the wound was still discharging, and the patient was obviously more ill : she had more headache, vomiting recurred, and the cerebellar signs which had been very slight a week after operation were becoming much more marked. Our supply of sulphonamide for intramuscular injection was exhausted on the sixteenth day, and two days later for the first time pneumococci were cultured from the cerebrospinal fluid A further supply for intramuscular injection was obtained, but despite this and increased dosage by mouth the patient gradually lost strength and developed profound cerebellar signs, and the spinal fluid became purulent with a free growth of pneumococci. She died on July 7, twenty-three days after operation. Necropsy showed a diffuse purulent meningitis, especially marked in the basal cisterns and cisterna magna.

It is worth recounting briefly the fate of the remaining seven cases in this first group. The methods of treatment employed are set out in Table I.

TABLE I

PRE-PENICILLIN GROUP

Method	No. of Cases	Recovered
1. Primary excision	1	0 (Case 2)
2. Decompression+aspiration	3	1 (Case 1)
3. Decompression+aspiration +excision	1	1*
4. Decompression	2	0
5. Fungus method	2	0
Total	9	2

* This was a fluid tuberculous abscess attached to the posterior aspect of the petrous bone having the clinical and radiological features of an otogenic abscess, but there was no history of aural infection nor any clinical or radiological evidence of such an infection. The pathology was not known until the abscess was excised, and further search failed to reveal a primary tuberculous lesion. This patient died from pulmonary tuberculosis three years after operation. It is thus probable that the abscess was a hæmatogenous one ; if so, it is the only one in this series not clearly due to mastoid infection.

Of the two fatal cases treated by decompression and aspiration, one died from meningitis which developed before operation. This patient was critically ill when she first came under observation, as much from meningitis as from the direct effects of the abscess, and as it was a streptococcal infection it might have responded to penicillin had that preparation been available. The other case died from increased intracranial pressure due to an undetected loculus ; one large loculus had been aspirated and outlined by thorotrast, but aspiration of it was not sufficient to deal with the problem of increased pressure in the posterior fossa. In retrospect we can infer from the deformity and displacement of the thorotrast shadow in the pyograms, that there was another loculus, but we did not know this at the time.

Two cases were treated by cerebellar decompression alone. One was a chronic thick-walled abscess (Fig. 4) which had been causing intermittent symptoms of increased intracranial pressure for five years. Although there was no papill-œdema and the spinal fluid was normal as to pressure and content, the correct diagnosis was made before operation on the grounds of a chronic infection of the left mastoid and a slight but definite left cerebellar deficit. It is worth noting that this patient tended to keep his head bent forward as in Case 1. A cerebellar decompression was done, and at a depth of 4 cm. the exploring cannula met a tough resistance which could not be pierced for aspiration. We hoped that the decompression would relieve the pressure symptoms and allow the abscess to enlarge posteriorly and thus make it more accessible for removal at a later stage. He did very well for twelve days after operation and then died suddenly. At necropsy there was no evidence of meningitis, but there was pronounced herniation of the cerebellar tonsils and upward herniation of the cerebellar vermis into the incisura tentorii (Fig. 5) due to a chronic left cerebellar abscess. This patient thus died from increased intracranial pressure rather than from infection.

The other patient treated by decompression had meningitis and pyæmia by the time of operation and died from a generalized infection. On admission he was moribund, but as the infection was staphylococcal it might have responded to penicillin.

In the two cases treated by the open or fungus

method the chain of events was similar. In each, the cerebellar abscess was initially aspirated through a mastoid wound; subsequently a cerebellar decompression and further aspirations were done. Signs of increased intracranial pressure and increase of the cerebellar dysfunction called for further aspirations, which were ineffective, so the wound was opened, the cerebellum overlying the abscess was excised, and the abscess was uncapped and allowed to drain on to the surface, the scalp and muscle being left open. In each case there were multiple loculi by the time this was done but subsequent necropsy showed that they had all been dealt with. Both patients died from subacute meningitis, one three and a half months after the original aspiration and two months after the creation of the fungus; the other two and a half months after the first aspiration and one month after the wound was left open. In one the infection was due to a gram-negative bacillus which was not sensitive to sulphonamides and might have resisted antibiotics; in the other, the responsible organism was a streptococcus, and although it did not yield to sulphonamide it might have responded to penicillin.

Thus, of the seven fatal cases it seemed that five died as the direct sequence of infection and two from increased intracranial pressure without any evidence of dissemination of the infection.

Cases Treated with the Aid of Penicillin

The introduction of penicillin has put an entirely new light on the problems set out above, as will be seen from the improved results in the second group (Table II). The methods of administering penicillin are described in a subsequent section.

TABLE II

PENICILLIN GROUP: NINE CASES OF CEREBELLAR ABSCESS (WITH PENICILLIN)

Method	No. of Cases	Recovered
1. Decompression+aspiration	2	1
2. Decompression+aspiration +excision	5	5
3. Primary Excision	2	2
Total	9	8

Of the two cases treated by decompression and aspiration one was almost identical with Case 1 above: two aspirations were required, and on each occasion penicillin was instilled into the cavity. There was a complete disappearance of symptoms and signs, and the pyograms showed that the abscess had shrivelled to a small mass stuck on to the posterior aspect of the petrous bone, as in Case 1 (Fig. 3). This patient has remained well for the twelve months which have elapsed since his treatment.

In the other case the patient died three days after operation from a combination of acute pulmonary infection and a post-operative clot. Intracranial infection seemed to play no part in his death, which we regarded largely as due to faulty operative technique.

Five cases were treated by excision after a preliminary decompression and aspiration, with instillation of thorotrast and penicillin at the time of aspiration. They were given systemic penicillin therapy as all of them had mastoid infections which had just been operated on or were thought likely to require operation. All these were so-called "acute" cases, like Case 1, with one exception, and this was a patient who had had a cerebellar abscess drained through a mastoid wound, with the subsequent formation of a fungus, in virtue of which he is included in the category of having had a decompression and aspiration. The fungus was granulating but bulging (Fig. 6, p. 6), and he was not acutely ill at any time before operation. After removal of the chronic abscess he developed acute meningitis due to *Ps.pyocyanea*, doubtless due to contamination from the fungus, but this responded to intrathecal administration of streptomycin.

In all except two of this group, the general condition of the patient improved so much after the initial decompression, aspiration, and instillation of penicillin that the operation for removal of the abscess could be undertaken as a deliberate procedure. One patient required a further aspiration before his condition improved to the point where the abscess could be left to our convenience. The other did not respond to a second aspiration, and the abscess had to be removed as an emergency measure. In this case the abscess ruptured and the field was grossly contaminated with streptococcal pus. There was slight post-operative meningitis which was controlled with penicillin and sulphadiazine, and the patient was discharged with the wound healed and the spinal fluid normal two and a half months after operation. He has remained well for the three years since operation.

On the whole the management of this group was so straightforward that we thought it worth trying primary excision, that is, at the first operation, rather than doing the preliminary decompression and aspiration. We were encouraged by the fact that in every case in which we had aspirated a cerebellar abscess there had been a perceptible capsule, that is, they were usually moderately chronic by the time they demanded treatment. Thus in Case 1, although

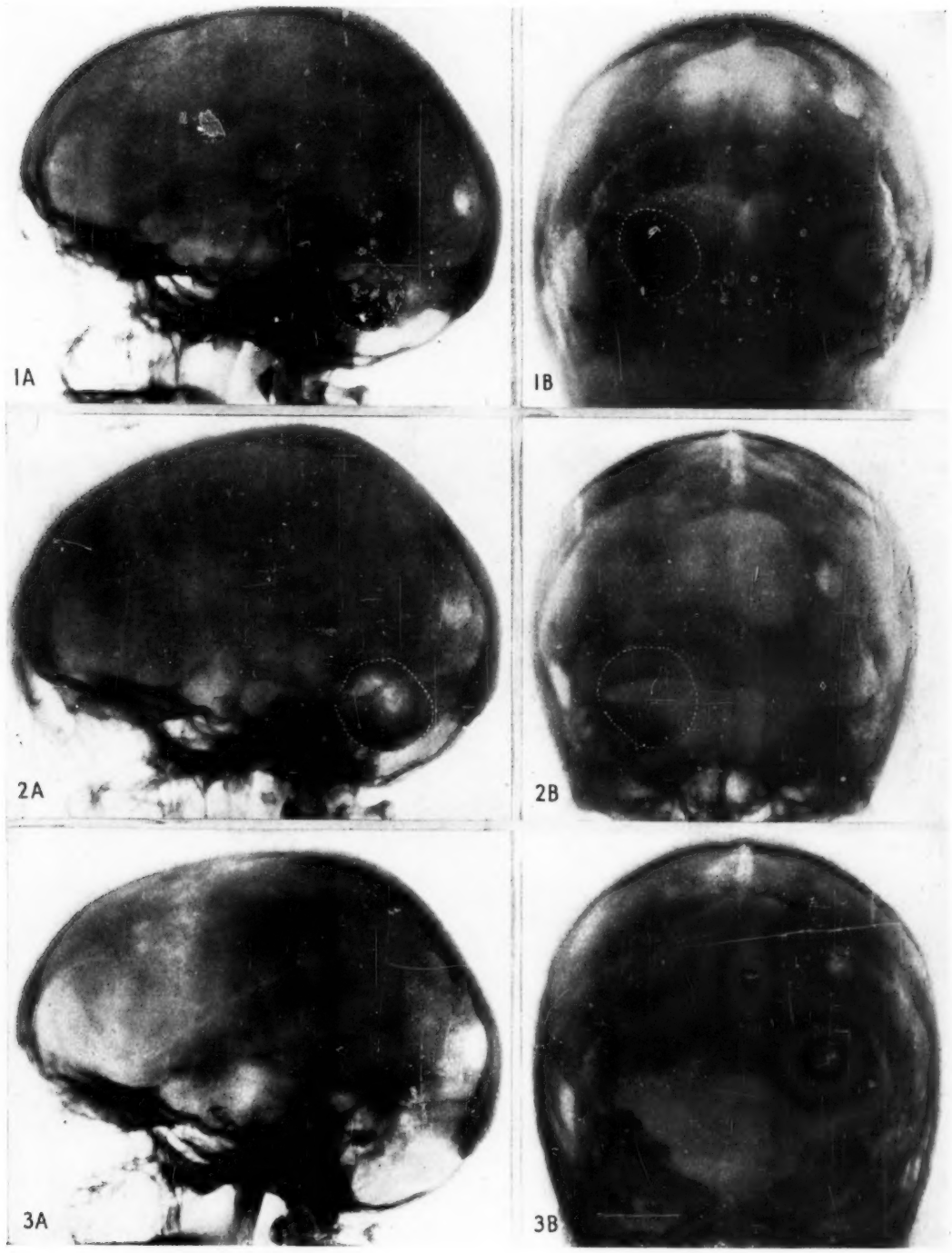

FIG. 1 A-B.—Case 1. Initial postoperative pyograms. The dotted lines outline the abscess.

FIG. 2 A-B.—Case 1. Pyograms five days later, showing increase in size of abscess.

FIG. 3 A-B.—Case 1. Pyograms three months after operation, showing the small thorotrast-encrusted mass adherent to the posterior surface of the petrous bone.

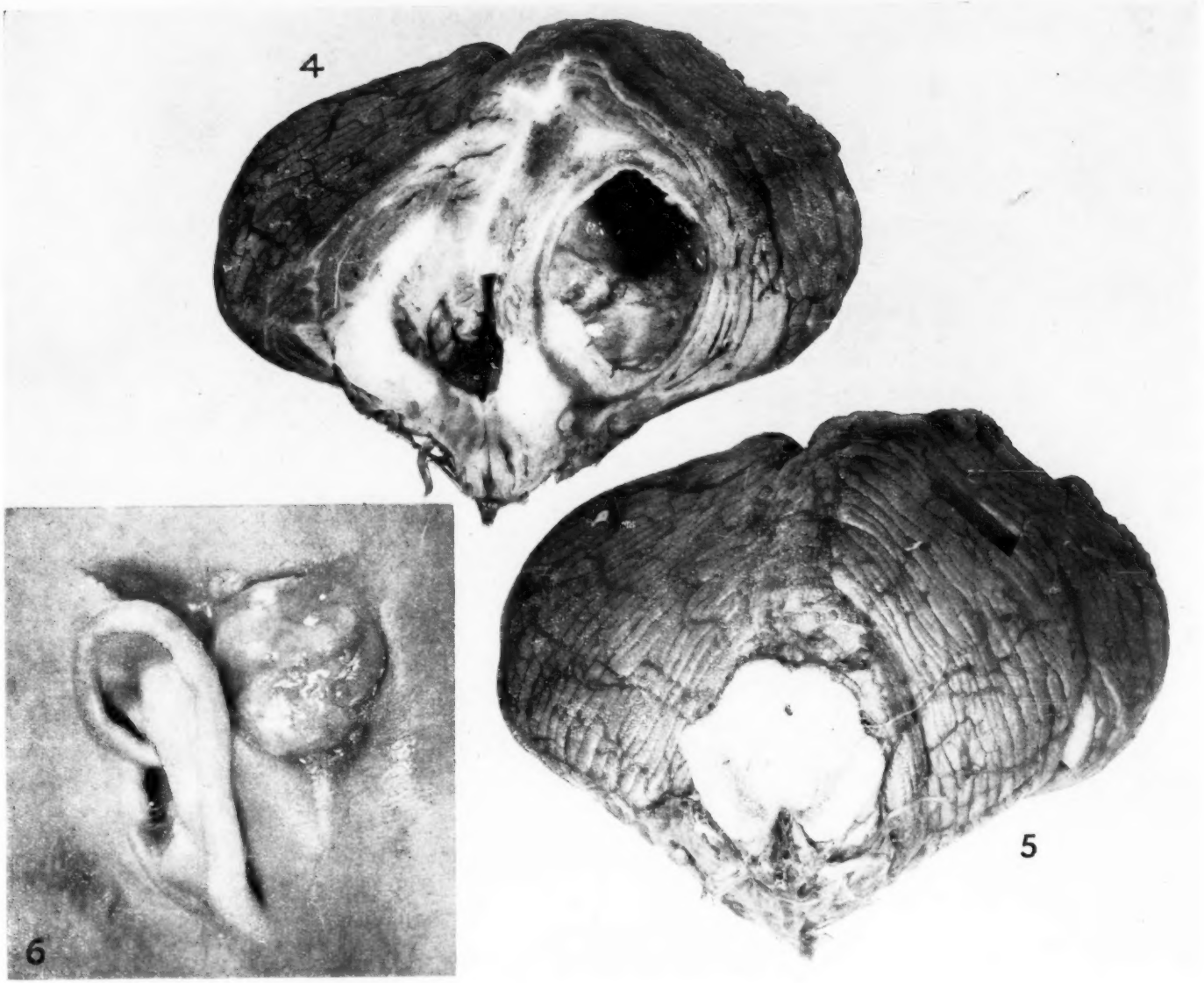

FIG. 4.—Chronic left cerebellar abscess which had been causing symptoms for five years.

FIG. 5.—Superior surface of cerebellum showing upward herniation of vermis and left cerebellar lobe along margin of midbrain caused by the abscess seen in Fig. 4.

FIG. 6.—Granulating fungus in a case of cerebellar abscess drained through a mastoid wound.

of midbrain caused by the abscess seen in Fig. 4.

FIG. 6.—Granulating fungus in a case of cerebellar abscess drained through a mastoid wound.

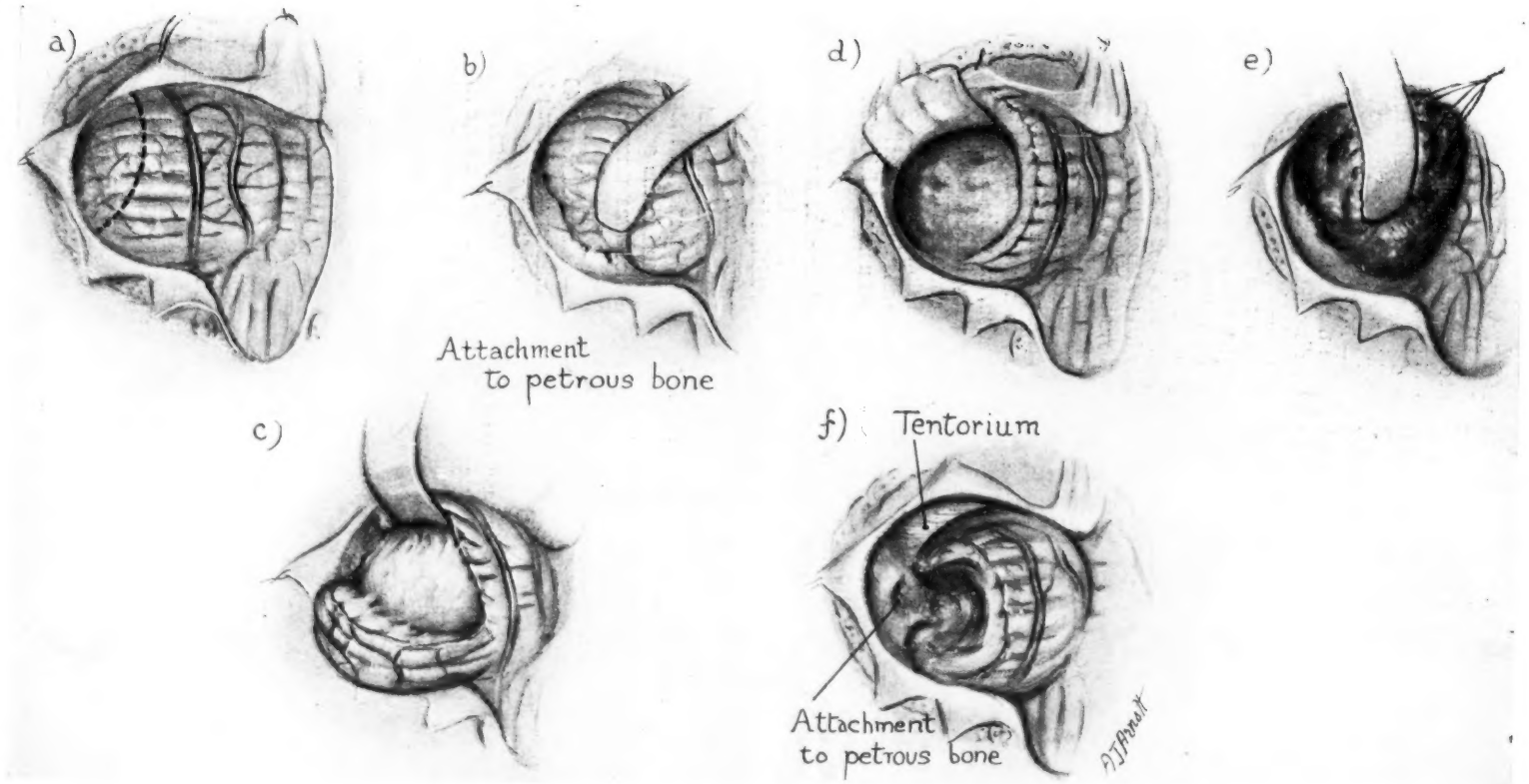

FIG. 7.—Operation sketches of excision of cerebellar abscess.

the patient was so acutely ill, the abscess was probably five or six weeks old by the time it was aspirated, and its capsule offered definite resistance to the exploring cannula. We have not seen a cerebellar abscess in the acute non-encapsulated stage, either at necropsy or operation and in this respect cerebellar abscesses seem to differ from other brain abscesses, which may cause urgent symptoms or death in the acute stage. It is the more remarkable because it would be expected that an acute infective focus in the small confines of the posterior fossa would have much more serious effects than a similar lesion above the tentorium. In the following case the abscess was removed within six days of the first manifest symptoms, although at operation it proved to have quite a tough capsule.

Case 3.—A man aged 31 years was admitted to the Ear, Nose, and Throat Department on Aug. 1, 1946. He had had bilateral discharging ears since the age of seven years, which had been treated intermittently with local applications. On June 12, 1946, he first came under observation in the E.N.T. Department. At this time he was complaining of a good deal of pain in and behind the right ear and there was an inflammatory swelling above and behind the ear. On the following day a radical mastoidectomy was performed, extensive disease being found in the mastoid. Convalescence was uneventful and he was discharged free from symptoms two weeks later, with instructions to report for outpatient dressings. He remained well until July 25, when he complained of feeling a " weakness " which manifested itself as unsteadiness in walking. On the following day his relatives noticed that his speech was a little slurred. He was due to report for a dressing on July 27, but was so unsteady on his feet that he could not leave his room. On the next day he complained of double vision and it was noticed that he had a squint. He vomited several times, but denied any headache or discomfort in his neck, complaining chiefly of the " weakness."

On admission to the E.N.T. Department, he was alert and seemed to be in no pain. The mastoid wound had healed and there was very little discharge from the meatus. There was pronounced slurring dysarthria, but no dysphagia. There was no stiffness of the neck nor any abnormality of posture. The optic fundi were normal. There was incomplete right external rectus paralysis, with slow, coarse nystagmus on looking to the right, rapid and fine on looking to the left. The right side of the face showed a slight weakness of the peripheral type. The right limbs were hypotonic and there was considerable ataxy and dysdiodokinesis, much more marked in the arm than in the leg. The spinal fluid pressure was 110 mm. and the fluid contained 150 mg. protein per 100 c.cm. and 150 white cells per c.mm., 72 per cent. of which were lymphocytes.

There seemed no doubt that he had a right cerebellar abscess, despite the absence of headache and of objective evidence of increased intracranial pressure. We have always regarded dysarthria as an ominous symptom in posterior fossa lesions, and partly because of this and partly because the other symptoms had come on so acutely we decided to operate at once. The cerebellum was exposed by the type of incision which we use for acoustic tumours. The folia of the right lobe were broad and pale, and a blunt needle encountered a resistance at a depth of 2·5 cm. A portion of the overlying cerebellum was resected to expose the capsule of the abscess, which proved to be up to 0·5 cm. thick, and it was dissected from the surrounding white matter. As in other cases, the dissection was made easier by aspirating the abscess, and stitching over the site of the puncture to prevent leakage and to provide traction strings. The abscess had a broad and firm attachment to the posterior surface of the petrous bone, and while this was being dissected the capsule burst and the residue of pus escaped into the field. This was sucked out, 10,000 units of penicillin solution (2,000 units per c.cm.) were left in the operative cavity, and the whole wound was dusted with penicillin sulphamezathine powder before closure.

Convalescence was uneventful. The wound healed by primary union and there was no evidence of meningitis. The patient was discharged three-and-a-half weeks after operation, at which time the nystagmus and external rectus palsy had cleared up, but there was still ataxy of the right arm and a little unsteadiness in walking. These improved slowly and were still noticeable one year after operation although he had been able to resume his former work as an unskilled labourer.

COMMENT.—The operative treatment of this case was almost identical with that of the only case of primary excision in the pre-penicillin group referred to above (Case 2). In both of them the field was grossly contaminated in detaching the abscess from the petrous bone. In the one this led to a fatal meningitis, and in the other, treated with penicillin, convalescence was uneventful.

Case 4.—A woman aged 40 was admitted to the Radcliffe Infirmary on March 29, 1947. She had had an acute mastoiditis on the left side in 1941 which had been dealt with by a radical mastoidectomy, after which she was deaf in the left ear but at no time subsequently had she ever had any earache or aural discharge. Five months before admission she had a child after a normal pregnancy. The puerperium was uneventful except that she could not feed the baby.

Four weeks before admission she began to complain of severe occipital headache, especially on the left side. Within a week this was followed by frequent vomiting and double vision. She was sent to another hospital, where, apart from deafness of the left ear, no neurological abnormalities were found. Two lumbar punctures were done : at each the pressure was normal or low (75 mm.), the fluid contained 40 mg. protein per 100 c.cm. and on one occasion 60 lymphocytes and on the other 30 lymphocytes per c.mm. While under observation she had agonizing headache, vomited repeatedly, and complained of giddiness if she moved her head ; if she tried to sit up in bed she fell to the left side. These signs suggested a rapidly expanding lesion and she was

accordingly transferred to the Nuffield Department of Surgery on March 29, 1947.

On admission, she was alert but complained of severe headache and resented any attempt to move her head. There was a slight slurring dysarthria but no dysphagia. The optic discs were normal. No ocular palsy could be demonstrated but there was slow coarse nystagmus on looking to the left, rapid and finer on looking to the right. The cranial nerve functions otherwise were normal. In the limbs, there was very slight hypotonia and ataxy of the left arm, only demonstrable in careful tests, and no definite abnormalities in the lower limbs. Radiographs of the skull revealed only the operative defect in the left mastoid region, with no evidence of recent infection.

Although the neurological signs were so slight, there seemed little doubt that she had a left cerebellar abscess. At operation on the following day the abscess was excised, the same technique being employed as in Case 3. The right ventricle was tapped before the dura was opened, and 12,000 units of penicillin were instilled. When the abscess was dissected off the petrous bone it was found that the dura also had been removed from an area about 1 cm. in diameter. The bare bone looked sclerotic but no pus was seen, and the field was not obviously contaminated at any time during the operation. Penicillin solution (10,000 units) was left in the operative cavity and the wound dusted with penicillin-sulphamezathine powder before closure.

Convalescence was uneventful. The headache was relieved at once, and the neurological abnormalities had completely disappeared by April 17, when the patient was sent to a convalescent home. She reported on May 14, six weeks after operation, free from any symptoms or signs, and she had returned to her normal activities.

COMMENT.—Of particular interest in this case was the genesis of a cerebellar abscess six years after a successful mastoid operation. It is possible that the intracranial infection occurred at the time of the mastoid operation and remained dormant for many years to flare up during a period of debility, such as might be expected after a pregnancy during a period of dietetic austerity.

Discussion

Cerebellar abscesses are treacherous, not only because they are infective but also because they behave in a less predictable way than other expanding lesions such as neoplasms in the posterior fossa. Thus in most of the cases described above there was little or no papillœdema, and the spinal fluid pressure was normal despite critical pressure relationships in the posterior fossa. Again, there was the experience of sudden death twelve days after a decompression operation without any symptoms or signs to suggest that this catastrophe was impending. For these reasons we only feel confident about a cerebellar abscess when it has been removed. There are exceptions, as in Case 1 and in one case in the second group, in which decompression and repeated aspiration brought about a complete recovery as shown by freedom from symptoms and signs. Schreiber (1941) has reported a series of eight cases in children treated successfully by a single aspiration. Even so we would not have been content to leave these abscesses had it not been that the pyograms showed that they had shrivelled up. In passing it should be said that the finding and removal of a small cerebellar abscess adherent to the petrous bone may be a matter of considerable technical difficulty, as we found in the case mentioned above which had been drained through a mastoid wound and subsequently developed a fungus. In this case we found it expedient to isolate the fibrous track at the base of the fungus and to follow it medially to the abscess.

Operative Technique.—We have employed the same operative approach in each case because we have found a remarkable constancy in the situation of these abscesses (Figs. 1–4, pp, 5 and 6). They are adherent to the posterior aspect of the petrous bone above and medial to the internal acoustic meatus. They expand posteriorly, and come to occupy the antero-superior part of the lateral lobe of the cerebellum. We have encountered only one departure from this situation, and this was an abscess in the superior vermis. In this case there was an infective thrombosis of the lateral sinus and torcula, and the cerebellar abscess seemed to result from a retrograde venous infection rather than by direct extension through the petrous bone as is usually the case.

The operation is thus similar to that which we employ for acoustic tumours ; and, as with these tumours, it is usually necessary to excise a portion of the lateral cerebellar lobe to expose the capsule. How much and what part of the lateral lobe should be excised to afford the optimum exposure can be determined by a study of the pre-operative pyograms, if they have been made, or by feeling the capsule with a blunt brain needle to see where it most nearly approaches the surface. Generally excision of the upper and lateral portion of the cerebellar hemisphere affords adequate exposure (Fig. 7, a, c, d). It is important not to carry the excision too far medially because of the risk of damaging the dentate nucleus : such a lesion produces a severe cerebellar disability which may be permanent.

Dissection is made easier by packing off the field, aspirating the abscess, and then stitching up the hole, using the sutures as traction strings (Fig. 7, e). This is analogous to gutting an acoustic tumour and it facilitates the deepest and most difficult part of the dissection, which is the detachment of the abscess from the dura over the petrous bone. The additional

room afforded by aspiration may also disclose other loculi and lessen the risks of rupturing them during the dissection.

The attachment to the dura over the petrous bone may be such that it can be scraped off by blunt dissection, or it may be so tough that it has to be cut off. In one case (Case 4) the dura was removed at the site of attachment, exposing a bare area of bone. This area was covered with a stamp of fibrin foam and no trouble ensued, although generally we would prefer to leave the dura intact. The fifth, seventh, and eighth cranial nerves are generally not seen, as the dural attachment of the abscess commonly lies lateral to the fifth nerve and above and medial to the internal acoustic meatus. No damage has been inflicted on cranial nerves in any of these cases.

As to the use of chemotherapy and antibiotics, we employ sulphadiazine and systemic penicillin before operation, and subsequently as dictated by the bacteriology of the abscess. Table III summarizes the bacteriological data in our series.

TABLE III

BACTERIOLOGY OF SIXTEEN CASES OF CEREBELLAR ABSCESS
(No Data in Two Cases)

	No. of Cases	Film +	Culture +
Pneumococcus	4	2	4
Anaerobic Streptococcus ..	3	3	3
Beta hæmolytic Streptococcus	1	1	1
Staphylococcus Aureus ..	2	1	2
Ps. Pyocyanea + Staph. Aureus	1	0	1
Gram-negative bacteria ..	2	2	0
Gram-positive cocci	1	1	0
M. Tuberculosis	1	0	(histology +)
Sterile	1	0	0

At the time of operation it is usually necessary to tap the lateral ventricle before opening the dura, and 10,000 units of penicillin are instilled. If the abscess is aspirated, 20,000 units in 1 c.cm. saline are instilled into the cavity whether it is being removed in one stage or left for subsequent removal. When the abscess is removed a further 10,000 units are left in the operative cavity, and the whole wound is dusted with penicillin-sulphamezathine powder. Any evidence of meningitis before or after operation may call for the intrathecal administration of penicillin if a sensitive organism is found to be responsible. If no organisms are found we rely on the parenteral administration of sulphonamides.

In one case post-operative meningitis due to *Ps. pyocyanea* was controlled by streptomycin. This was the case with the fungus mentioned above (Fig. 6), and there was clear evidence of meningitis five days after operation, although the organism was not recovered from cultures until the twelfth day. Lumbar punctures were very difficult in this case, so we punctured the loculation in the posterior fossa and instilled the streptomycin by this route. Forty thousand units were used on the first occasion, and as there was no ill effect 80,000 units were instilled daily for seven days. The fluid was sterile after the first injection and remained so subsequently. The protein content diminished from 300 mg. at the beginning of the infection to 60 mg. at the end of the streptomycin treatment and the cell count dropped from a maximum of 3,500 per c.mm. to 0.

In none of our cases were there any fits or other untoward results of the use of antibiotics.

As these abscesses are usually due to mastoid infection, the question of treatment of the mastoid often arises. In some cases a patient with an untreated mastoid infection first comes under observation when he develops a cerebellar abscess, and the problem of priority of treatment has to be decided between the aural surgeon and the neurological surgeon. We have not found the decision to be a particularly difficult one in the majority of cases : the lesion which is the more immediate danger to life should be dealt with first. In three of our cases this meant an urgent cerebellar decompression and aspiration or removal of the abscess, depending on the patient's general condition. The mastoid infection should then be dealt with as soon as possible. As the retro-auricular incision commonly employed in mastoid operations is usually just in front of the lateral limb of the cerebellar operation, our otological colleagues, Mr. R. G. Macbeth and Mr. G. Livingstone, have usually employed the permeatal route with satisfactory results.

It is more common for the cerebellar abscess to require treatment sometime after a mastoid operation. If the classical route has been used the mastoid scar may be incorporated in the lateral limb of the scalp incision if it has healed soundly. If it has not healed, whether clean or suppurating, we prefer to stay away from it, and open the posterior fossa by a middle line incision. This approach can be used for decompression and aspiration to tide over a crisis, but would probably be inadequate

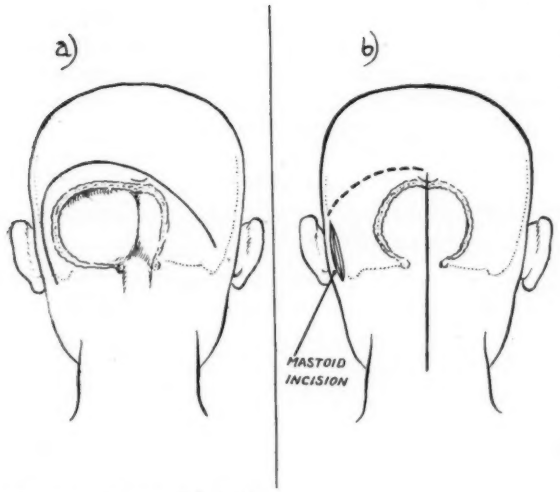

FIG. 8.—Types of incision :
(*a*) if there is no mastoid wound ; (*b*) if the mastoid wound has not healed.

for removal of the abscess. In the one case in which we employed this method, the decompression and aspiration relieved symptoms for three weeks, by which time the mastoid wound had healed soundly. The vertical middle line incision was then joined to the mastoid one to make an inverted U-shaped flap suitable for a unilateral cerebellar operation (Fig. 8).

Functional Results.—Of the ten patients who have recovered, seven have been left with no demonstrable neurological deficit, and they professed complete freedom from symptoms. They have all returned to full work, or in the case of children are proceeding normally with their education.

In three of the cases treated by excision there were residual disabilities of the ipsilateral limbs. In one unsteadiness of gait and profound ataxy of the right arm prevented the patient from returning to his work as a farm labourer, but he supports himself by working as a tea-boy for a construction company. In another, there was very slight unsteadiness of gait and ataxy of the right arm which did not impair the patient's efficiency as an unskilled labourer. In the third there is a gross residual ataxy of the left arm and leg, but it is too early to assess his potentialities as he was only discharged four months ago and is still having re-educative exercises. In each of them there were technical difficulties at operation and probably more trauma was inflicted than is necessary in most cases : two were multilocular abscesses adherent to the side of the brain stem, and one was the fungus case mentioned above. Nevertheless, two of them were cases which were obviously not going to respond to decompression and aspiration and there seemed to be no alternative to excision.

Diagnosis.—In conclusion we should like to add a short note about diagnosis. The nearly constant location of these abscesses means that the neurological picture is usually very similar, the differences being in degree. Headache, often severe, was almost constant with the notable exception of Case 3. It may be generalized or referred to the occipital region on both sides, or chiefly on the side of the lesion as in Case 4. Vomiting and giddiness are common, and in association with headache during a mastoid infection should always raise the question of an intracranial abscess. Few of the patients complained of subjective visual disturbances, and as most of them were confined to bed they were not aware of any ataxy of their limbs.

Objectively, we were struck by the frequency with which these patients tend to keep their heads bent forward, almost as though they were trying to pull the cerebellar tonsils out of the foramen magnum. This is just as ominous a posture as the more common opisthotonic one seen in cases of intracranial tumours, and it is remarkable that it can occur without papillœdema or any increase in the spinal fluid pressure, as in several of the cases mentioned above.

The invariable abnormality was nystagmus, as with acoustic tumours. It is slow and coarse on looking to the side of the lesion, rapid and finer on looking to the other side. It was often associated with weakness of conjugate ocular movement on looking to the side of the lesion, as pointed out by Symonds (1927).

Trigeminal impairment and facial weakness were rare. The degree of deafness was usually determined by the nature of the mastoid infection and operative intervention, but sometimes it is greatly increased and bilateral as a result of pressure of the abscess on both auditory nerves.

Dysarthria was common in the acute stages and seemed to be more a factor of inco-ordination than palatal or pharyngeal paralysis. We regard it as an ominous symptom in abscesses and tumours, and in abscesses in particular it is usually an indication for urgent treatment.

In the locomotor system, the most frequent findings were ataxy of the limbs on the side of the lesion and this was usually much more marked in the arm than in the leg. In some cases it was gross and could not be missed ; in other cases it was very slight and could only be demonstrated by formal tests.

In the vast majority of cases there were abnormalities in the cerebrospinal fluid, either an increase

in the protein or a pleocytosis or both. Lumbar puncture may be a dangerous procedure in acute cases and we have usually refrained from doing it until immediately before operation.

Radiographs of the skull have been of no particular help in diagnosis other than showing evidence of the mastoid infection if that was not already known.

In only three of the eighteen cases was the diagnosis in sufficient doubt to make ventriculography necessary. In each of these there was moderate dilatation of the lateral and third ventricles indicating a lesion in the posterior fossa. In one the aqueduct and fourth ventricle could be seen to be displaced to the side opposite the lesion.

We think it important to emphasize the clinical features of cerebellar abscess, because any of the symptoms or signs mentioned above, or any combination of them, in a patient suffering from mastoiditis calls for urgent neurological diagnosis. We believe that the management of the abscess should be the responsibility of the neurological surgeon, and that he should see the patient as soon as possible when intracranial complications are suspected. We consider that exploratory aspiration of the cerebellum through a mastoid wound is generally inadvisable, and that it is preferable to approach the abscess through a clean field as described above. Drainage of an abscess through a mastoid wound is also undesirable because more often than not it will be ineffective, and if a temporary improvement does occur it is usually at the expense of the formation of a fungus which adds considerably to the difficulties and dangers of dealing with the residual abscess.

Summary

1. The diagnosis and treatment of eighteen cases of cerebellar abscess are described.

2. Of the first nine cases treated by various surgical procedures without penicillin, two recovered.

3. Of the second nine cases treated by similar surgical procedures with penicillin, eight recovered.

4. In the majority of the successful cases the abscess was excised, although in two cases recovery followed decompression and repeated aspiration of the abscess.

5. It is suggested that, with the aid of antibiotics, excision of cerebellar abscess is a reasonably safe procedure and is the treatment of choice.

REFERENCES

Kahn, E. A. (1939). *Arch. Neurol. Psychiat. Chicago*, **41**, 158.
Sachs, E. (1946). *Ann. Surg.*, **123**, 785.
Schreiber, F. (1941). *Ibid.*, **114**, 330.
Symonds, C. P. (1927). *J. Laryng.*, **42**, 440.
Vincent, C., David, M., and Askenasy, H. (1937). *J. Chir., Paris*, **49**, 1.

OBSERVATIONS ON THE CAUSE AND MECHANISM OF SYMPTOM-PRODUCTION IN SCIATICA AND LOW-BACK PAIN

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INTRODUCTION

The ætiology of sciatica and low-back pain is still a matter of controversy. A wide range of lesions has been put forward to explain these two conditions, often without much evidence to support them. The purpose of this study is first to investigate the relation of these symptoms to lesions of the intervertebral disc, and secondly to elucidate the way in which the symptoms are produced.

For this purpose two parallel groups of cases were studied. The first group comprised 100 consecutive patients suffering from disabling sciatica or low-back pain submitted to operation with a presumptive diagnosis of disc protrusion. These patients were referred to a neurosurgical unit from many hospitals after failure of medical treatment in their particular hospitals, and hence must be regarded as forming a highly selected group. They will be described as the " surgical " group. At operation, intraspinal disc prolapses were found and dealt with in all but one case, and relief or improvement of symptoms followed in the majority, establishing that the disc prolapses had been the common cause of symptoms in this group. The second group consisted of 76 patients with severe sciatica or low-back pain, who, because they comprised almost all such cases admitted to a single general hospital from its own particular district, must be regarded as representative of the great mass of sufferers from sciatica and low-back pain. They were admitted initially to medical wards, where they were treated conservatively, and therefore will subsequently be referred to as the " medical " group. A number of them, however, still remaining incapacitated after medical treatment, were later submitted to surgery, and 36 of them are included in the first group. Each of the two groups, when taken as a whole, presented similar clinical symptoms and signs, and

similar findings indicating disc prolapse on myelography, suggesting that disc prolapse was the common cause of symptoms in the second group, as in the first. Myelography, however, when repeated after recovery in those cases in which symptoms subsided without operation, indicated that the disc prolapses were still there. This led us to make further inquiries, and our observations will now be discussed in more detail.

OBSERVATIONS ON ÆTIOLOGY OF SCIATICA AND LOW-BACK PAIN

A. In " Surgical " Cases of Sciatica and Low-Back Pain

The myelographic and operative findings in this group have already been discussed in some detail (Begg, Falconer, and McGeorge, 1946 ; Falconer, McGeorge, and Begg, 1948). The patients were referred to us for surgical treatment from many parts of New Zealand during a period of two years. Before operation most had had complete rest in bed for a month or more without relief of disabling symptoms. In 77 of the hundred cases in this group intractable sciatica was the predominant symptom, and in each of these disc prolapses were found and dealt with at operation, with improvement or relief of symptoms in every case, although in some instances more than one operation was required. This indicates that disc lesions are the cause of symptoms in this group (Falconer and others, 1948). In the remaining 23 cases, severe low-back pain predominated or occurred alone, and in all but one of these disc prolapses were shown at operation to be present, while improvement or relief of symptoms followed in all but two. During the period in which this group of 100 cases was being collected, only two other cases with sciatic pain of a severity and intractability necessitating operation came under our notice, and in both of these tumours affecting the cauda equina had caused the symptoms. We concluded, therefore, that disc prolapses must be the only common cause of sciatica which is both severe and intractable, and also probably, of severe and intractable low-back pain.

Myelography was performed before operation in 95 of the " surgical " cases, although in the cases of " sciatica " the diagnosis was based upon clinical findings alone, and, if the clinical signs were deemed sufficient, operation was carried out whether the myelogram was positive or negative. A positive myelogram, however, was required before operation was undertaken in the presence of low-back pain alone (Falconer and others, 1948). In 9 cases the findings were obscured by artefacts due to faulty technique, leaving 86 cases which were examined satisfactorily. In 88 per cent. of these the myelographic appearances were deemed pathological, and subsequently at operation the level of the disc prolapse was confirmed in almost every instance (74 out of 76 cases). Only in 12 per cent. of cases were the myelographic appearances considered normal. We concluded, therefore, that myelography could demonstrate disc lesions in most cases, and that when it was positive it was reliable. A negative myelogram, however, does not exclude a disc lesion.

B. In " Medical " Cases

During a period of three and a half years commencing with, but extending beyond, the period in which the " surgical " cases were being collected, approximately 400 patients were seen by us through the courtesy of our colleagues, mostly as out-patients, from the city and rural district immediately surrounding the hospital. These patients by and large presented the same histories and the same signs as did the " surgical " cases, but in most instances the symptoms were milder or else responded to domiciliary treatment. Some 83 cases in this series, however, had severe symptoms which necessitated their admission to hospital, and it is from these 83 cases that our second group is taken. Some had complained of symptoms intermittently for many years and for long periods at a time ; others had developed their first symptoms only recently. Many had previously received physiotherapy without lasting benefit, but very few had been treated by complete rest in bed for more than a week or two. As the only difference between these cases and those not admitted to hospital was one of severity of symptoms, we may regard this group of in-patients as representative of the great mass of sufferers with sciatica and low-back pain, whose symptoms are disabling but who have not yet received adequate medical treatment.

All cases in this " medical " group were examined by myelography according to the same technique as the surgical group and were then treated conservatively by complete rest in bed for at least four weeks, either in hospital, or, after investigations were completed, in their own homes. Of the 83 cases, 7 can be excluded from further consideration, 2 of these because the myelograms were obscured by artefacts, and 5 because their symptoms and disability were dubious. These 5 cases were all seeking compensation for back pain referable to an injury, and had no definite physical signs, normal radiographs of the spine, and normal myelograms.

This leaves 76 cases suffering from leg and/or low-back pain, which were examined satisfactorily by myelography and which were studied in our second group. In 52 cases sciatica predominated,

in 2 anterior crural pain was present, while in the remaining 22 cases low-back pain predominated or occurred alone. All cases showed physical signs, such as exacerbation of pain on coughing or sneezing, rigidity of the lumbar spine, limitation of straight-leg raising, although in some these signs were only slight. In respect of physical signs, however, this " medical " group of cases was essentially similar to the " surgical " group. Of the 76 cases, 32 (42 per cent.) recovered without operation and have since remained symptom-free, whereas 44 (58 per cent.) either failed to respond to rest in bed or else, after a period of temporary remission, again developed recurrent symptoms and were then submitted to operation. Thus approximately 1 in 9 of the " medical " cases we were asked to see was eventually treated surgically, and a disc lesion was demonstrated in almost every case.

Myelography revealed abnormalities indicative of disc protrusions in 88 per cent. of these cases (67 cases), while no abnormality was discovered in 12 per cent. (9 cases). As the frequency with which myelography revealed positive findings is the same as in the operated group, it is difficult to come to any conclusion other than that disc protrusions must have been present in the " medical " cases in the same proportion as in the " surgical " cases, that is, in practically every case. The confirmation of disc prolapse in each " medical " case which eventually came to operation and the subsequent improvement in symptoms supports this deduction.

OBSERVATIONS ON MECHANISM OF SYMPTOM-PRODUCTION

Granted then that disc prolapses are of almost universal occurrence in cases of sciatica and low-back pain, the question next arises as to how they produce symptoms. In this connexion we have collected a number of observations that appear relevant.

A. Concerning Disc Prolapses

1. Operative Findings.—In the course of our operative experience we have noted that when symptoms of sciatica are present the disc prolapse is so situated that it abuts upon a nerve root in its course lateral to the theca, either the fifth lumbar nerve at the level of the fourth lumbar disc or the first sacral nerve at the fifth lumbar disc. However, when low-back pain occurs alone, the disc prolapse is so situated that, although it may indent and compress the theca, it does not involve a nerve root in its extrathecal course. The roots of the cauda equina within the theca are mobile and can slip away from any lesion narrowing the theca, unless it be large enough to occlude the thecal lumen completely. The extrathecal nerve roots, however, are more fixed in their short course between two anchoring points, the point at which each emerges from the theca, and the point at which each passes into the intervertebral foramen. Consequently the extrathecal nerve root cannot easily slip away from a disc protrusion (O'Connell, 1943).

2. Stimulation under Local Anæsthesia.—The presence of a disc prolapse alone will produce low-back pain, but some degree of nerve-root compression is necessary to produce sciatica. In a few patients with sciatica and low-back pain operated on under local anæsthesia, we found that pressure with a probe on the disc prolapse reproduces low-back pain, whereas pressure on either the fifth lumbar or first sacral nerve root reproduces sciatic pain.

3. Fluctuations in Size.—The size of many, though probably not all, disc protrusions fluctuates with the degree of weight-bearing and other torsional strains imposed upon the affected disc. We have for example shown, both at operation and by myelography, that the prominence of many prolapses is increased by hyperextension of the spine and also by weight-bearing, particularly in the class of disc prolapse which we term " intermittent." Knutsson (1942) appears to have made similar observations in cadaver specimens. Thus in recumbency the size of many disc protrusions is less than during activity.

4. Position in Relation to Theca and Nerve Roots.—The siting of a disc prolapse in relation to the theca and nerve roots is governed by anatomical arrangements (Falconer, 1944). Most intraspinal disc prolapses protrude to one side of the posterior longitudinal ligament, and when situated at the fourth and fifth lumbar interspaces have an opportunity of compressing extrathecal nerve roots, for these are the only two spaces which are customarily crossed by nerve roots in their extrathecal course (Fig. 1). Sometimes the fourth lumbar nerve in its course lateral to the theca comes into relation with the third lumbar disc, and a laterally placed protrusion here may lead to anterior crural pain. Most disc prolapses, however, at this and higher levels are so placed that they cannot produce nerve-root compression, and consequently they remain symptomless or cause only back pain. Again, we have operated on a few cases of low-back pain and found a large disc prolapse at the fourth lumbar level which was not causing sciatica, presumably because in these particular cases the fifth lumbar nerve roots on either side emerged through the theca below the level of this disc.

In a smaller proportion of cases the disc prolapse is situated in the midline anterior to the theca. Such

cases are commonly characterized by repeated attacks of low-back pain, and do not exhibit sciatica unless the disc prolapse is sufficiently broad to extend far enough laterally on one or both sides to implicate a nerve root situated lateral to the theca. As might be expected, such broad central prolapses are often associated with bilateral sciatica. In some cases pain is present in both legs simultaneously. In other cases it alternates from one leg to the other, presumably secondary to slight alterations in the contour of the prolapse, which bulges slightly more, first to one side and then to the other. Occasionally a patient is encountered who can voluntarily change both the direction of his sciatic scoliosis and the side of his pain by wriggling and twisting his lumbar spine.

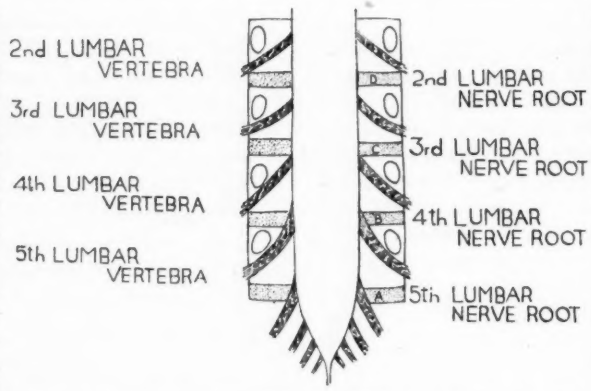

FIG. 1.—Illustrating topography of the lumbar theca and extrathecal nerve roots in relation to the intervertebral discs. Note that the extrathecal fifth lumbar and first sacral nerve roots cross the fourth and fifth lumbar discs respectively. A prolapse at sites A and B is likely to cause extrathecal nerve root compression, but not at sites C and D.

5. Myelographic Observations after Spontaneous Disappearance of Symptoms.—The suddenness with which symptoms may appear or pass off, particularly in sciatica, but also in low-back pain, would seem to suggest that disc prolapses may appear suddenly, and reduce themselves equally as rapidly. Undoubtedly this does happen, especially when a disc prolapse, as for example an extrusion, develops immediately after a sudden and severe trauma, while certain disc prolapses can be shown by myelography to alter in size with changes in the torsional strains applied to the back (Begg and others, 1946). Moreover, post-mortem studies of human spinal columns have indicated that gradual healing of posterior disc prolapses can occur (Beadle, 1931 ; Rabinovitch, 1947). But a noticeable alteration in the size of a disc prolapse does not always accompany the appearance or disappearance of symptoms in sciatica or low-back pain, and in this connexion we have made an unexpected set of observations, namely that when symptoms pass off either spontaneously or after rest in bed the disc prolapse often persists apparently unchanged in size.

This observation was made in 10 patients admitted to the medical wards with acute symptoms of recent onset, who all recovered rapidly and completely with rest in bed (Table I). Each had characteristic clinical signs, and when examined during the period of symptoms each showed positive myelographic evidence of a disc prolapse. Subsequently, at periods varying from one to fifteen months after cessation of symptoms, myelography was repeated, and in most instances the radiographic silhouette of the disc protrusion was found to have persisted unaltered. Only in the patient, in whom the myelogram was repeated fifteen months after recovery from symptoms, did the appearances suggest a slight recession in size.

Fig. 2 gives an example of the usual myelographic findings. They are from a 45-year-old man (first case in Table I) admitted with an 11 weeks' history of left anterior crural pain associated with marked scoliosis. Symptoms cleared completely within a few days of admission to hospital. This set of myelograms shows that at the time of acute symptoms he had, in addition to a disc prolapse, swelling of the involved nerve root, but that after symptoms had ceased the swelling of the nerve root disappeared, although the disc prolapse remained the same size.

6. Operative Observation after Spontaneous Disappearance of Symptoms.—In an operated case, not included in this subgroup, we had the opportunity of making a similar observation. This was a man who had had sciatica persistently for eighteen months without being benefited by long periods of rest in bed. A myelogram showed a disc prolapse, but a few hours later all symptoms suddenly disappeared. Next day the man discharged himself from hospital, but within forty-eight hours he was back again with a severe recurrence. Three days later his symptoms again disappeared, but myelography when repeated showed the disc prolapse to be still apparently unaltered. The patient asked for operation, and in due course a typical disc projection at the fourth lumbar space was found and removed. The nerve root was noted to be easily movable over the prolapse and not taut. Since operation the patient has remained symptom-free for four years.

It would seem then that the spontaneous disappearance of symptoms in sciatica or low-back pain is not necessarily due to the disappearance of the disc prolapse, and furthermore that a disc prolapse may be present without symptoms. Similarly, although in many instances a sudden onset of symptoms is undoubtedly due to a sudden

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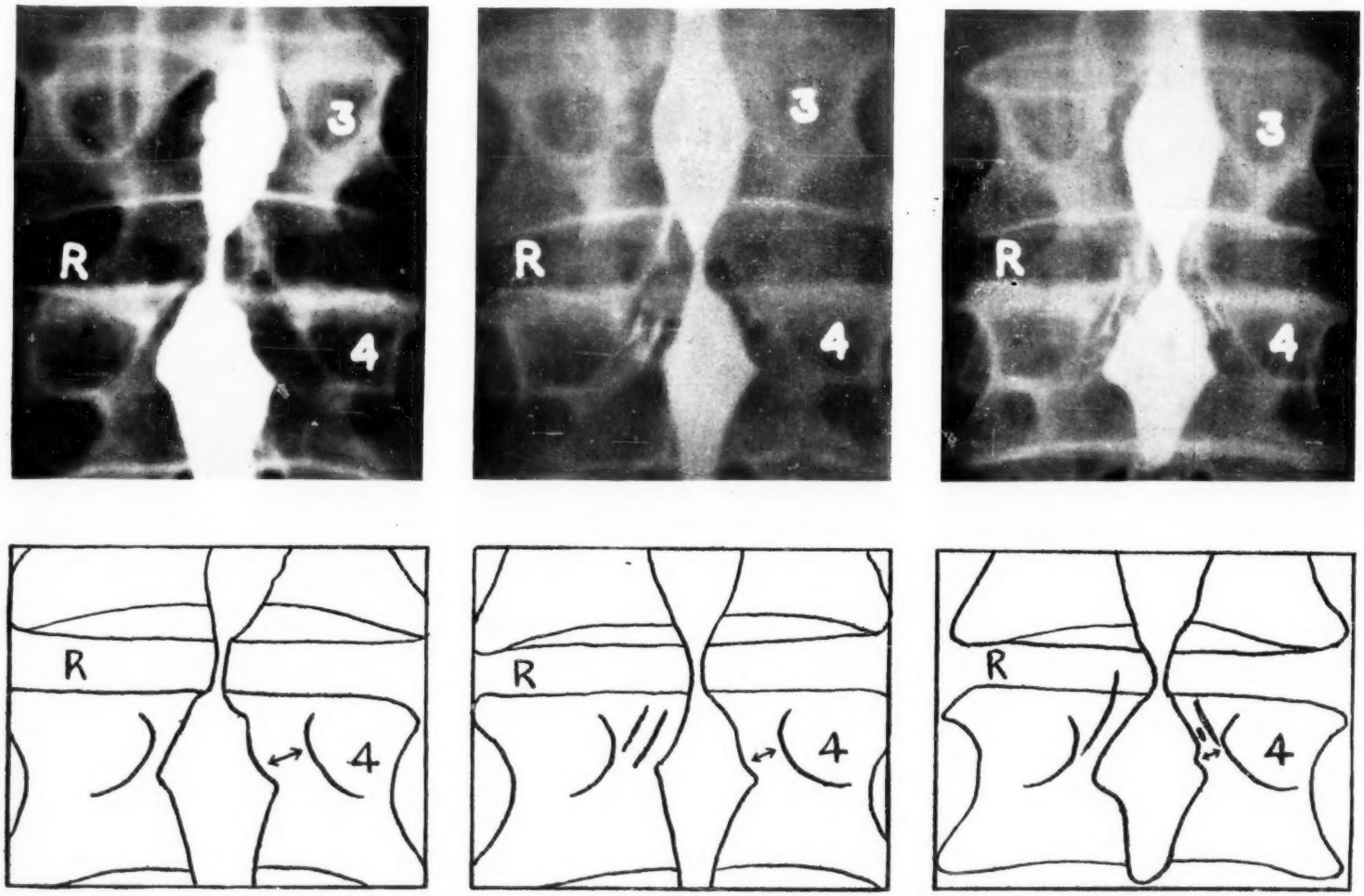

FIG. 2.—Myelograms of a patient with left anterior crural pain who recovered spontaneously. The first film was taken during the height of symptoms, while the second and third films were taken 2 weeks and 2 months respectively after all symptoms had subsided. Note that in the first film a deformity indicating a central prolapse at the third lumbar space can be seen, and in addition a displacement of the thecal column suggesting a swollen fourth lumbar nerve root (indicated by double-head arrow in the underlying diagram). In the second and third films the deformity due to the disc prolapse persists unchanged, while the size of the nerve root has apparently returned to normal.

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Sex	Age	Leading symptom	Duration of leading symptom	Disability		Myelogram			Later progress
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M	31	Sciatica	4 weeks	Unable to work	Symptom-free	Prolapse L 4	Unchanged	1 month	3 years—symptom-free ; heavy work
M	42	Low back pain	2 hours	Bed-ridden	Symptom-free ; full work	Prolapse L 4	Unchanged	9 months	2½ years — occasional slight pain ; steady light work
M	37	Back + leg pain	6 weeks	Unable to work	Symptom-free	Prolapse L 4	Unchanged	1 month	2½ years — occasional back pain ; steady light work
M	58	Sciatica	4 weeks	Unable to work	Symptom-free	Prolapse L 3	Unchanged	1 month	2½ years — symptom-free ; heavy work
F	18	Low back pain	3 weeks	Intermittent severe pain	Symptom-free ; full work	Prolapse L 4	Unchanged	8 months	1½ years — symptom-free ; steady moderate work
M	32	Sciatica	3 weeks	Bed-ridden	Symptom-free ; heavy work	Prolapse L 5	Similar but smaller	15 months	1¼ years — symptom-free ; steady moderate work
F	43	Low back pain	2 days	Bed-ridden	Symptom-free ; heavy work	Prolapse L 3	Unchanged	11 months	9 months — symptom-free ; heavy work
M	28	Sciatica	3 weeks	Bed-ridden	Symptom-free ; full work	Prolapse L 5	Unchanged	8 months	8 months — symptom-free ; steady moderate work
M	48	Sciatica	5 weeks	Walks with difficulty	Symptom-free	Prolapse L 3 + 4	Unchanged	3 weeks	4 weeks—symptom-free; not working

development of a disc prolapse, particularly after severe trauma, it seems likely that some disc prolapses are present long before symptoms arise. This possibly occurs in some cases of low-back pain or sciatica, in which symptoms begin suddenly for no obvious reason, as in patients sitting comfortably at table or lying quietly in bed, where trauma does not appear to play any part. Again, in the case quoted in the preceding paragraph, the sudden recurrence of symptoms after the patient's first discharge from hospital took place in the presence of a disc protrusion known to be already present. Disc prolapse, however, is but one of the two requisites for the production of sciatica, and it is now opportune to pass on and discuss the role of the nerve roots.

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1. Operative Findings.—We have already stated that, in our "surgical" patients, whenever there were symptoms of sciatica the disc prolapse was found to be so situated that it could impinge upon a nerve

root in its extrathecal course. Often the extrathecal nerve root was flattened, but generally it appeared macroscopically normal. Sometimes on opening the theca the ventral and dorsal components of the involved nerve would together appear congested and swollen to a varying degree, and for a varying extent above and proximal to the orifice of the dural sleeve, through which they leave the theca. This appearance has been noted by others (Holmes and Sworn, 1945 ; Munro, 1945, etc.) and considered by them as evidence of a primary radiculitis. We, however, have always found in such cases that the nerve root was compressed by a disc prolapse just distal to its point of emergence from the theca.

2. Stimulation under Local Anæsthesia.—As stated earlier, during operations under local anæsthesia we have also observed that pressure on either the fifth lumbar or first sacral nerve root with a probe causes radiating crural pain akin to sciatica. Furthermore, we have observed during pre-operative investigations that infiltration of the affected nerve with a local anæsthetic solution at the point where it crosses the disc prolapse will relieve all pain and also such signs as limitation of straight-leg raising (Falconer, Glasgow, and Cole, 1947). Indeed, the infiltration of the extrathecal nerves at each interspace in turn can be used as a diagnostic procedure to determine at which interspace the disc prolapse lies, although the procedure is too formidable for routine use.

3. Transmission of Impulses through Affected Nerve Root.—In association with our colleagues in physiology (D. Malcolm and F. H. Suckling) we investigated at operation in several patients the speed of transmission of impulses down the affected nerve root as compared with the intact roots, and also the amplitude of the resulting muscular contraction. In this investigation the motor nerve root proximal to the lesion was stimulated intrathecally with a single electric shock of graduated intensity, and the resulting contractions in the calf and foot muscles were recorded electrically by means of surface electrodes placed over the muscles. The action potentials were recorded with a specially constructed amplifier and double-beam oscilloscope incorporating a suitable time marker. Slight delays in conduction of up to 2 milliseconds were sometimes observed in the affected nerve root, while the amplitude of the muscle contraction was usually less. These observations indicated that the degree of blocking of nerve impulses passing through the compressed segment of nerve root was usually only slight. It is this slight blocking of the conduction of impulses through the compressed segment of nerve root, however, which presumably accounts for the neurological features such as slight muscle weakness, slight sensory impairment, and diminution of the ankle jerk, which characterize most cases of sciatica.

4. Complete Blocking of Impulses.—In occasional cases, however, a complete block of the nerve root occurs, leading to such symptoms as foot-drop or cauda equina paralysis. We have observed four cases of foot-drop, and have evidence that the lesion here is a complete blocking of the conduction of impulses through a single nerve root.

In three cases the muscles almost completely paralysed were the tibialis anticus and extensor longus hallucis, while the extensor longus digitorum and the peronei were weakened. In all three the fifth lumbar nerve root was found compressed at operation. We had the opportunity of stimulating the nerve roots at operation in one of these cases, and found that the fifth lumbar nerve root alone would not conduct impulses, whereas the first sacral nerve root conducted normally.

In the fourth case the paralysed muscles included the peronei and the extensor longus digitorum, while the extensor longus hallucis and tibialis anticus muscles were only weakened. The posterior calf muscles and the long flexors of the toes were also markedly weakened in this case, and at operation the first sacral nerve root was found to be involved by a disc prolapse.

All four cases of foot-drop had a characteristic feature in that there had been one or more attacks of sciatica culminating in a very severe episode of pain, which passed off completely but left them with the foot-drop. It seems reasonable to presume that the very severe episode of pain was caused by pressure on the nerve steadily increasing until the nerve was blocked completely, producing muscular and sensory paralysis and also cessation of pain because the nerve root could no longer conduct impulses or be stimulated at the point of compression. In two of our cases some degree of recovery followed slowly after operation. A somewhat similar, but rare, sequence of events is seen in cauda equina paralysis, where a large centrally-placed disc prolapse may invaginate the anterior wall of the theca to such an extent that it compresses the cauda equina.

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dermatome. These signs are generally well known, although the full extent of the dermatomal patterns has seldom been realized (Falconer and others, 1947). Other common signs include aggravation of pain on coughing or sneezing, rigidity and flattening of the lumbar spine, and limitation of straight-leg raising.

6. Significance of Certain General Signs.—One of the most characteristic signs in sciatica and low-back pain due to disc protrusion is exacerbation of pain on coughing or sneezing. This is of course a feature of "root pain" in general. Those who have observed, either at operation under local anæsthesia or more readily during the performance of myelography, the sudden distension of the theca which accompanies these movements, will readily appreciate how sudden and presumably painful angulating strains are provoked in any extrathecal nerve root which may straddle a disc protrusion. Also any sudden jarring movement of the spinal column may alter the tensions within the disc prolapse itself, and in a proportion of cases will affect its size.

Rigidity and flattening of the lumbar spine are seen in many cases of low-back pain occurring by itself, as well as in most cases of sciatica. The rigidity results from spasm of the spinal muscles, and presumably is a protective reflex mechanism designed to splint the lumbar spine in a position where the degree of prominence of a disc prolapse is lessened and any further torsional strains which might increase its size are avoided. The flattening results from some degree of obliteration of the normal lumbar lordosis, and presumably is due to the same mechanism. Begg and others (1946) have shown, both at operation and by myelography, that extension of the lumbar spine will increase the backward prominence of some disc protrusions. The splinting of the spine in a position of slight flexion probably obviates this latter factor.

7. Observations on Straight-Leg Raising.—Another characteristic and paramount sign of sciatica is the limitation of straight-leg raising, and we have made two parallel sets of observations on its mode of production which help to explain much of the pathogenesis of sciatica. The first set of observations was made on a few patients with sciatica during operations performed under general anæsthesia. These patients were placed on their sides and the disc lesion was exposed. As the straight-leg raising test was carried out, the affected nerve root was found to tighten over the summit of the protrusion, in many instances burying itself into the protrusion. It was noted that the distance which the extended leg had to be flexed at the hip before appreciable tension developed within the nerve root corresponded roughly to the degree of limitation of straight-leg raising present before operation. Thus, in cases where this sign had been markedly positive, only a slight degree of flexion at the hip caused the nerve root at the level of the prolapse to be pulled downwards, whereas in cases where this sign was less marked a greater degree of hip flexion could be made before appreciable longitudinal tension developed within the nerve root.

In order to elucidate these phenomena we made a second set of observations on the post-mortem table. In three cadavers, all examined within two hours of death and before rigor mortis had set in, we removed the lumbar laminæ and tested the effects of the straight-leg raising manœuvre on the cauda equina. On performing this test we observed that the fifth lumbar and first sacral nerves moved downwards through their respective foramina distances of from 2 to 6 mm., and that this movement did not begin until the leg was flexed about 30° to 40° from the table, and was greatest as the leg was moved from 60° to 90° of flexion. The fourth lumbar nerve moved downwards to a lesser extent, and the remaining lumbar nerves did not move at all. Inman and Saunders (1942) have reported similar observations.

A striking difference between these observations on cadavers and our observations on living subjects was that in patients in whom limitation of straight-leg raising was marked the downward migration of the fifth lumbar and first sacral nerves would begin after a much smaller movement of the hip. We therefore repeated our observation on cadavers, after tying a string round each extrathecal nerve root at its junction with the theca and connecting the string to a spring balance (Table II). If a constant longitudinal tension of 400 g. was applied to the nerve in order to take up the slack, we found that as the hip was flexed to a right angle the first sacral nerve would be pulled downwards for a distance of up to 12 mm. through its intervertebral foramen, while the nerves above it would be pulled down for successively shorter distances until the third lumbar nerve, which did not move at all. If movements of the nerve roots through the intervertebral foramina were prevented, a longitudinal strain of up to 3·2 kilos (7 lb.) would develop within the first sacral nerve root, and proportionately lesser strains with the other roots. We also measured the breaking strains of the extrathecal roots, and found that a longitudinal tension of approximately 4·6 kilos (10 lb.) would snap the first sacral nerve, a strain which was not much greater than the strain of 3·2 kilos (7 lb.) developing in the nerve when its downward movement was prevented.

8. Types of Strain Involving Affected Nerve Roots.—Now this state of affairs is paralleled by what occurs in sciatica due to intervertebral disc prolapse. The prolapse restricts the free movement of the fifth lumbar and first sacral nerve root through their respective intervertebral foramina, especially when the prolapse is wedged in the angle between the extrathecal nerve root and the theca. Often

TABLE II

EFFECTS OF STRAIGHT-LEG RAISING TO A RIGHT ANGLE ON LUMBAR AND SACRAL NERVE ROOTS IN THE CADAVER

Nerve root	Distance traversed by nerve root (under ½ lb. strain)			Longitudinal strain developed if nerve root is held fixed			Breaking strain of nerve root		
	1st body	2nd body	3rd body	1st body	2nd body	3rd body	1st body	2nd body	3rd body
1st sacral ..	0·5 in. (13 mm.)	0·5 in. (12 mm.)	0·5 in. (12-mm.)	7–7·5 lb. (3·2–3·4 kilo)	7 lb. (3·2 kilo)	7 lb. (3·2 kilo)	10 lb. (4·6 kilo)	8 lb. (3·6 kilo)	10 lb. (4·6 kilo)
5th lumbar ..	0·4 in. (10 mm.)	0·3 in. (8 mm.)	0·4 in. (10 mm.)	5·5–6 lb. (2·5–2·7 kilo)	5 lb. (2·3 kilo)	6·5 lb. (3 kilo)	10 lb. (4·6 kilo)	6·5 lb. (2·9 kilo)	7 lb. (3·2 kilo)
4th lumbar ..	0·3 in. (8 mm.)	0·2 in. (5 mm.)	0·2 in. (5 mm.)	4–5 lb. (1·8–2·3 kilo)	2·5 lb. (1·2 kilo)	2 lb. (0·9 kilo)	6 lb. (2·7 kilo)	5 lb. (2·3 kilo)	6 lb.. (2·7 kilo)
3rd lumbar ..	0·2 in. (5 mm.)	— —	— —	1–1·5 lb. (0·5–0·7 kilo)	0·5 lb. (0·2 kilo)	0·5 lb. (0·2 kilo)	? ?	6 lb. (2·7 kilo)	5 lb. (2·3 kilo)
2nd lumbar..	— —	— —	— —	— —	— —	— —	? ?	5 lb. (2·3 kilo)	? ?

also there are adhesions between the prolapse and the nerve root. The prolapse consequently produces strains of three types within the nerve root—a longitudinal strain described above, perhaps a compressive strain by squeezing the nerve root between the prolapse in front and the ligamentum flavum behind, but most important of all an angulating strain within the nerve root as it is pulled taut and bent over the prolapse. It is this latter type of strain which is probably mainly responsible for symptoms. Thus our colleagues in physiology, Dawbin and others (1947), who experimented on the effects of these various types of strain on the conductivity of nerve trunks, have shown that angulating strains of a given intensity are more effective in blocking the conductivity of nerve trunks than are longitudinal or compressive strains. Similarly those who have observed nerve trunks exposed in patients during operations under local anæsthesia, or particularly posterior nerve roots within the theca, know that these structures can be submitted to an appreciable degree of longitudinal strain without producing pain, but the moment they are forcibly angulated or are pinched considerable pain is experienced by the patient. This pain the patient refers, not to the point where the nerve is compressed, but to the zone of distribution of the nerve. The same phenomenon undoubtedly occurs in sciatica, and the shearing strains within the nerve at the point of angulation set up impulses within the nerve fibres which travel both up and down the nerve. The afferent impulses in the pain fibres of the nerve on reaching the spinal cord are relayed to the sensorium, and the sensorium naturally interprets them as coming from the peripheral endings of the pain fibres in the distribution of the affected nerve root.

9. Significance of Straight-Leg Raising Test : Evidence for Variations in Length of Affected Nerve Roots.—The actual limitation of straight-leg raising in cases of sciatica is of course due to spasm of the hamstring muscles, and this would seem to result from a reflex-mechanism initiated by increases in the strains within the affected nerve root, for the limitation can be abolished by injecting and paralysing the affected nerve root with a local anæsthetic solution where it crosses the disc prolapse (Falconer and others, 1947). Clinically the degree to which straight-leg raising is limited in sciatica is roughly proportional to the severity of a patient's pain (Falconer, 1944). As the patient's pain decreases when recovery occurs spontaneously or after operation, the restriction of straight-leg raising becomes proportionately less until the hip can be flexed to a right angle or more. It would seem, then, that when limitation of straight-leg raising is slight, as in cases with mild symptoms or those recovering spontaneously, there must be some slack in the nerve root which is not present in the more severe cases. We know that nerve roots can lengthen spontaneously, for Dawbin and others (1947) have observed this in experimentally produced sciatica. In a series of cats they placed a small block of wood or wax under the lowest nerve root in a position similar to that ocupied by a disc

prolapse in man. Immediately after the block was inserted, the nerve root straddling it was always taut, but two or more weeks later when the animal was either re-explored or killed, the nerve root was always found to be slack, even though the block was still *in situ*. Furthermore, whereas immediately after operation the animal might limp, within a few days the limp would disappear.

There are grounds, therefore, for assuming that, as symptoms of sciatica wear off the involved nerve root elongates and slackens; for, as described earlier, the disc prolapse itself often does not subside. Conversely we may presume that when symptoms suddenly flare up in the presence of a pre-existing prolapse, some change has occurred within the nerve which tightens it and reduces the amount of slack. This change may be caused merely by slipping of the nerve root on to the summit of a prolapse. More often, probably, some sudden temporary increase in size of the disc prolapse, brought about by changes in posture of the spine or by weight-bearing, may cause the prolapse to impinge upon a nerve root, leading to intraneural contusion and œdema, which then tightens it.

10. Observations in Case of Sciatica due to a Hydatid Cyst.—In a unique case of sciatica due to a hydatid cyst (Falconer and others, 1948), we found evidence which supports the view that attacks of sciatica are more directly related to changes within the nerve roots than to the appearance of a disc protrusion. In this patient several recurrent attacks of sciatica had occurred, each initiated apparently by a fall. The hydatid cyst arose in the body of the first piece of the sacrum and projected into the extrathecal space. It was protected everywhere from external violence by bony structures. Moreover, before operation the hydatid complement fixation and Casoni cutaneous reaction were negative, indicating that the thin-walled cyst had never leaked into the host's tissues. Therefore, as the hydatid cyst itself had undoubtedly not been affected by trauma, we can only presume that the appearance of symptoms after each fall must have been provoked by changes within the nerve roots straddling the cyst.

11. Nature of Pathological Changes within Affected Nerve Roots.—Information regarding the precise pathological changes present in sciatica within the sciatic nerve and its roots is scanty, but the known facts are consistent with the above view regarding symptom-production. The few histological reports which have been made (Denny-Brown, 1933; Wilson, 1940; McKenzie, 1947) indicate that the pathological change is one of œdema rather than infiltration by an inflammatory exudate. In most instances, however, the sciatic nerve trunk seems to have been examined, and in only one case could we find a report concerning the changes within the compressed nerve root (Adams, quoted by McKenzie, 1947). It would seem that this œdema can extend some distance up and down the nerve from the point of compression, and as stated earlier we have frequently seen at operation marked swelling of components of the affected nerve root within the theca. It is interesting that in McKenzie's case œdema of the nerve root was demonstrated histologically, although no swelling was visible to the naked eye. Undoubtedly this œdema of the nerve root and nerve trunk is analogous to that observed experimentally by Weiss (1943) and by Denny-Brown and Brenner (1944) occurring both above and below a chronic compression of a nerve trunk, and which Denny-Brown and Brenner hold is due to vascular congestion consequent upon an impairment of the blood supply of the nerve. It is our surmise that œdema within a nerve causes it to swell, and that as the nerve swells in diameter it shortens in length, and vice versa.

In addition to our observations on disc prolapse and nerve roots we made a number of other observations, largely of a negative kind, which are relevant to this discussion.

C. Other Observations

1. Significance of Trauma.—We feel that some authorities have overemphasized the importance of sudden trauma in the causation of intervertebral disc protrusions. Undoubtedly it does play a part in some cases, but Schmorl and his associates (Beadle, 1931) pointed out that a premature senescence of tissues was the principal factor in producing disc degeneration, and that this was aided by "the slight shocks of normal life." This senescence may begin in some discs shortly after puberty, leading to desiccation of the nucleus pulposus and to fissuring and thinning of the annulus fibrosus. This ageing process affects the various discs throughout the spinal column to varying degrees, so that while some may degenerate early others are spared for a long time. The constantly recurring stresses and strains of an active life undoubtedly contribute to this ageing process, but, as Hyndman (1946) and others have stressed, a single severe traumatic strain is unlikely to lead to a prolapse of an intervertebral disc, unless the disc is already degenerate. Indeed, the vertebral body will fracture before a normal disc will rupture. Our own observations support this point of view, for we have already shown in the group of operated

cases that a history of possible antecedent trauma was obtainable in only 44 out of the hundred patients.

2. Significance of Scoliosis.—Scoliosis is often seen in cases of sciatica, and when marked is often labelled " sciatic scoliosis." It was noted in exactly half our " surgical " cases, and in each instance was associated with a disc prolapse of either a projection or an extrusion type (Falconer and others, 1948). In no instance was it associated with a disc prolapse of the intermittent type (the " concealed " disc of Dandy), and the fact that the scoliosis was always associated with a prolapse which remained fixed in the spinal canal and was not reducible by relaxation or by postural manœuvres must surely be of some significance. The mechanism of scoliosis is presumably one of spasm of the spinal muscles designed to splint the affected disc space in the position where the disc prolapse exerts the least possible strain on surrounding structures, particularly those with nerve filaments sensitive to pressure.

We, however, were unable to correlate the direction of the scoliotic curvature with the side of the symptoms, although we did make some observations of significance. Three examples of scoliosis occurred in cases of low-back pain without any leg pain, and as only 10 patients in the " surgical " group had never had even a trace of leg pain, the proportion of cases of scoliosis in this small minority is roughly the same as in the group with leg pain. This suggests that sciatica or nerve-root compression is not a requisite feature for " sciatic scoliosis " to develop, but that the disc prolapse alone is required. This view seems to be supported by our failure to correlate the direction of scoliosis and the side of the symptoms in cases with sciatica. Thus of the cases with unilateral sciatica, in 25 the convexity of the primary scoliotic curve was directed to the same side as that of symptoms, while in 17 it was directed to the opposite side. Yet in both these subgroups there were instances where the summit of the disc prolapse was situated lateral to the compressed nerve root, and instances where it was situated medial to the nerve root. In 5 cases alternating scoliosis was present, and it is probably significant that in all 5 the summit of the disc prolapse was situated in the midline anterior to the theca, while in 3 of these cases the symptoms of sciatica also alternated from one leg to the other. After operation these scoliotic deformities disappeared in every instance.

3. Level of Protein in Cerebrospinal Fluid.—The protein level is sometimes raised in the cerebrospinal fluid in cases of sciatica or low-back pain, and we attempted to correlate this with a number of factors, but without success. In 3 of our " surgical " cases the protein level was over 100 mg. per 100 c.cm., in 23 cases it was between 50 and 100 mg., while in 74 cases it was normal (below 50 mg.). Most of the lumbar punctures were performed between the third and fourth lumbar spines. There did not seem to be any constant relationship between the protein level and such features as the duration of symptoms, the severity of symptoms, the type of disc prolapse, the situation of the disc prolapse in relation to the theca and extrathecal nerve roots, or the presence or absence of nerve-root compression. Unfortunately for the solution of this problem the theca was opened in only a few cases, so that we were usually unable to correlate the protein levels with the appearances of the cauda equina. We noticed, however, that some of the cases with swelling and congestion of the intrathecal portion of the affected nerve roots, and even some with marked leptomeningeal adhesions (meningitis serosa circumscripta) had normal protein levels. The only definite observation was that, whenever a complete blocking of the thecal column was demonstrated by myelography, the protein content of the cerebrospinal fluid was raised. However, in this particular series of operation cases such a block was demonstrated only on three occasions.

4. Miscellaneous Observations.—Following Kellgren's work (1939) on the production of segmental pain by injecting small quantities of hypertonic saline into deep somatic structures, particularly the interspinous ligaments, some workers have been inclined to ascribe the pain of sciatica as a segmental or reflex pain due to lesions of the ligamentous structures in relation to the lower lumbar interspaces. Kellgren's work, however, has not to our knowledge yet been confirmed by other workers, and in a few patients we attempted to produce segmental pain by injecting hypertonic saline into the interspinous ligaments, but without success.

In a few of our cases of sciatica tender spots which could be described as " nodules " were observed in the muscles of the buttock and calf, and in one or two instances temporary relief of symptoms appeared to follow their infiltration with local anæsthetic solution. Some clinicians have considered these nodules to be evidence of " fibrositis," although in our case-material we always found an associated disc prolapse. Elliott (1944) recently has shown by means of electromyography that these " nodules " are due to localized areas of involuntary muscle spasm. Their precise significance, however, is still unknown.

In 30 of our early cases detailed blood examinations were performed, including leucocyte counts

and blood sedimentation rates, without any abnormality being shown. Furthermore, in only 2 instances in the whole series was a white cell count of more than 5 cells per c.mm. observed in the cerebrospinal fluid. Consequently, we were unable to obtain the customary evidence of an inflammatory disease which would deserve the appellation of " sciatic neuritis " or of " fibrositis."

DISCUSSION

Sciatica and low-back pain are two separate clinical conditions, although they may occur together, and sciatica is commonly preceded by low-back pain. Their order of occurrence may also be reversed, and either may occur independently. Therefore they are presumably caused by different mechanisms.

Evidence has been produced to show that a disc prolapse by itself can cause low-back pain. The posterior part of the annulus fibrosus, the posterior longitudinal ligament, and the extradural veins and other related structures are presumably supplied with sensory nerve fibres by the sinu-vertebral nerve of Luschka, which has been described in great detail by Hovelacque (1927). Attention has again been drawn to it by Roofe (1940). This nerve, which is a tiny recurrent twig arising from each spinal nerve, leaves its parent nerve distal to the spinal ganglion and, after uniting with a component branch from the sympathetic ganglionated chain, re-enters the spinal canal through the intervertebral foramen. According to Roofe and to Bradford and Spurling (1941) the type of terminal arborization of these nerve fibres suggests that they subserve pain sensibility. Presumably, then, low-back pain is due to involvement of these fibres by the disc prolapse, while the associated physical signs such as rigidity of the lumbar spine and the scoliosis noted in a proportion of cases are produced by reflex muscle spasm as a protective mechanism, designed to restrict the degree of movement occurring at the affected disc space and so to lessen the severity of the pain.

Evidence has also been advanced to show that the pain of sciatica is produced when a disc protrusion impinges upon a nerve root. The nerve root in its turn becomes œdematous, undergoing slight longitudinal shortening. As it straddles the disc prolapse, it is pulled tight against the prolapse particularly during flexion movements of the trunk and spine, while also the height of the prolapse may be increased by weight-bearing and torsional movements of the spine. The affected nerve root may then be subjected to strains of various types—longitudinal, compressive, and angulating—but it is particularly the angulating strains which provoke afferent impulses in the dorsal component of the nerve root, that pass upwards to the spinal cord, and then are relayed on to the sensorium where they produce a sensation of pain referable to the distribution of the nerve root.

The production of sciatica thus depends upon the association of two factors, the presence of a disc prolapse, and changes within the nerve root. In the absence of one or the other there may be no symptoms. As regards the two factors considered independently, we believe that, although the disc prolapse may be the primary ætiological lesion, the production of crural pain and other neurological features is more directly related to the intrinsic changes within the nerve root than to the prolapse, because if at any time, or in any manner, the longitudinal tension within the nerve root, as it lies in contact with the prolapse should lessen, symptoms will improve. This hypothesis of symptom-production in sciatica and low-back pain can also explain why these conditions, although they may occur as early as the second decade of life or as late as the seventh, most commonly occur in the fourth and fifth decades, for these are decades when disc degeneration and prolapse are usually well developed, and when the average man and woman are still leading an active and vigorous life. It should also be remembered that Andrae, working in 1929 at Professor Schmorl's Institute at Dresden, showed that posterior disc protrusions appeared with increasing frequency with advancing years, and were seen in 15·2 per cent. of 368 spinal columns examined post-mortem (Beadle, 1931).

There are of course other proven causes of sciatica besides intervertebral disc prolapse, although they are rare, but this hypothesis can be readily adapted to include them. In the course of our operative experience we have occasionally encountered tumours of the cauda equina or of the spinal column, granulomatous disease of the intervertebral disc, and spondyloliothesis causing sciatica (Falconer and others, 1948). Tumours of the cauda equina and spinal column, for example, can act as struts against which a nerve root may be strained. It is interesting that in these cases symptoms of sciatica may be intermittent, even though the primary lesion is continuously present (as in a case of hydatid cyst referred to earlier in the text), and this supports our hypothesis that the production of symptoms is more directly related to the changes within the nerve root.

The value of an hypothesis is that it should serve as a foundation upon which to build a rational system of therapeutics. Many forms of treatment have been tried, some of which will now be considered. Experience shows that, when symptoms of sciatica and low-back pain are mild, a patient may

often recover without special treatment, and with an ambulatory regime. Presumably in such circumstances the intrinsic changes within the nerve roots subside spontaneously, or perhaps the nerve root slips off the summit of the disc or the adhesions which may bind it to the disc give way in response to some slight trauma. When, however, symptoms are severe, only two forms of treatment need be seriously considered, namely rest and operation.

It is a great principle of therapeutics in all parts of the body to rest the injured part. Bed-rest is the usual application of this principle to sciatica, and acts both by lessening the repeated impacts of the nerve against the disc prolapse, and also in many instances by lessening the size of the protrusion through withdrawing weight-bearing. We have customarily treated our patients in the first instance by at least one month's complete rest in bed, and only if that failed have we advised surgical treatment. Many authorities, however, practise an even more positive form of rest, and immobilize the spinal column of their patient in a plaster body cast or on a Bradford frame for similar or longer periods of time. It may be argued that this is a more effective form of rest to the spine than that afforded by rest in bed, but we have no experience on which to decide this point.

Operative treatment, we feel, should be reserved only for those patients in whom treatment by rest for an adequate period of time has been tried without benefit or with only temporary relief, and in whom the disability is appreciable, so that they are unable to pursue their work in a reasonable manner. We have shown that, when performed in accordance with certain principles, the results of surgical treatment are satisfactory. There is, however, in many quarters a feeling that " once a disc protrusion, then always a disc protrusion," and that if a disc prolapse can be diagnosed now, it should be operated on, because if not the patient will develop trouble again later. Many authorities for instance state that the mere demonstration of a disc prolapse by myelography is good grounds for operation (Poppen, 1945), but we personally do not think so. Any clinician of experience can recall numbers of patients who, after suffering from a bout of severe and protracted sciatica with signs suggesting disc prolapse as the cause, became relieved of symptoms, and never subsequently suffered a recurrence (Ekvall, 1939 ; Dunning, 1946). Although in the short period of time in which we repeated our myelograms in the group of 10 " medical " patients who obtained relief by bed-rest, evidence of regression in the size of the prolapse after disappearance of symptoms was not forthcoming, except in one case, regression nevertheless probably occurs frequently over the years. Indeed Rabinovitch (1947), in a series of spinal columns examined post-mortem, has made striking histological observations of " healing " of degenerate discs by fibrous scarring and even by bony ankylosis, while Beadle (1931) also indicates that this can occur. The pessimistic attitude concerning the late results of conservative therapy which prevails in certain quarters is therefore without foundation.

Still other forms of treatment have been recommended, but we feel that these are not as effective or as certain in their response as the two we have just considered. Manipulation of the spine under anæsthesia and stretching of the sciatic nerve by open operation may possibly act by stretching the affected nerve root and so elongating it. Perhaps it is not without significance that these procedures are occasionally followed by transient or permanent foot-drop, suggesting that the nerve has been stretched to the point of rupture. The epidural injection of large amounts of saline may act by shifting the nerve root in relation to the prolapse or by stretching it. Finally the so-called negative explorations with subsequent and unexpected cure reported by many surgeons in cases of suspected disc lesion may be examples of intermittent prolapse (Falconer and others, 1948), in which the retraction of the nerve root consequent upon an exposure of the disc space has stretched or shifted the nerve root sufficiently to relieve symptoms.

This hypothesis of the mechanism of symptom-production in sciatica and low-back pain, then, can explain most of the features of these two conditions, and can also be correlated with the mechanisms by which the standard therapeutic procedures probably lead to relief. We feel that upon it we can justify our belief that the treatment of intervertebral disc prolapse should in the first instance be conservative, and that surgical methods should be adopted only when conservative measures have failed.

In conclusion we may state that we have been unable to confirm the validity of such older hypotheses advanced to explain sciatica and low-back pain, as " fibrositis and sciatic neuritis " (Gowers, 1899), " sacro-iliac strain " (Baer, 1917), " arthritis of the spinal inter-articular joints " (Putti, 1927), or " contracture of the fascia lata " (Ober, 1935).

SUMMARY

Routine myelography performed in patients suffering from sciatica or low-back pain, admitted to hospital because of severity or intractability of symptoms, has indicated that intraspinal lumbar disc protrusions are present in almost all cases, whether the patient will later recover from symptoms

spontaneously, or only after the operative removal of the disc prolapse.

Myelography, when repeated after spontaneous recovery from symptoms has occurred, usually shows that the intraspinal disc prolapse persists apparently unchanged.

A number of further clinical observations are reported, which indicate that low-back pain is caused by the disc prolapse alone, presumably through implication of the sinu-vertebral nerve of Luschka, and that sciatica occurs only when the disc prolapse is so situated that it impinges upon a nerve root in its extrathecal course, at the level of either of the lower two lumbar intervertebral discs. Secondary changes, probably of intraneural œdema, appear within the affected nerve root, which contribute to the production of symptoms by pulling the nerve root tight against the disc prolapse, thereby causing angulating and other strains within it. These strains in their turn excite afferent impulses within the nerve, which on reaching the sensorium produce a sensation of pain referable to the peripheral distribution of the affected nerve root. A slight blocking in conductivity through the compressed segment of nerve root accounts for the associated muscular, sensory, and reflex disturbances. The spontaneous remission of symptoms, which often occurs in sciatica, can result from a resolution of the neural changes without an associated resolution of the disc prolapse.

In treating sciatica and low-back pain conservative measures applying the principle of rest to the lumbar spine should always be tried in the first instance, and are often successful. Surgical treatment should only be considered when conservative measures fail and disability is appreciable.

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References

Baer, W. S. (1917). *Johns Hopk. Hosp. Bull.*, **28,** 159.
Beadle, O. A. (1931). "The Intervertebral Discs." *M. R. C. Spec. Rep.*, No. 161. London.
Begg, A. C., Falconer, M. A., and McGeorge, M. (1946). *Brit. J. Surg.*, **34,** 141.
Bradford, F. K., and Spurling, R. G. (1941). "The Intervertebral Disc." Springfield, Illinois.
Dawbin, W., Cole, D. S., and Glasgow, G. L. (1947). (Personal communication.)
Denny-Brown, D. (1933). *Proc. roy. Soc. Med.*, **26,** 1399.
——, and Brenner, C. (1944). *Arch. Neurol. Psychiat., Chicago*, **52,** 1.
Dunning, H. S. (1946). *Ibid.*, **55,** 573.
Elliott, F. A. (1944). *Lancet*, **1,** 47.
Ekvall, S. (1939). *Acta med. Scand.*, **101,** 1.
Falconer, M. A. (1944). *N. Z. med. J.*, **43,** 58.
——, Glasgow, G. L., and Cole, D. S. (1947). *J. Neurol. Neurosurg. Psychiat.*, **10,** 72.
——, McGeorge, M., and Begg, A. C. (1948). *Brit. J. Surg.*, in press.
Gowers, W. R. (1899). "Manual of Diseases of the Nervous System." London
Holmes, J. M., and Sworn, B. R. (1945). *Brit med. J.*, **2,** 350.
Hovelacque, A. (1927). "Anatomie des nerfs craniens et rachidiens et du système sympathique chez l'homme." Paris.
Hyndman, O. R. (1946). *Arch. Surg.*, **53,** 247.
Inman, V. T., and Saunders, J. de C. M. (1942). *Radiology*, **38,** 669.
Kellgren, J. H. (1939). *Clin. Sci.*, **4,** 35.
Knutsson, F. (1942). *Acta Radiol.*, **23,** 431.
Lindblom, K. (1944). *Ibid.*, **25,** 195.
McKenzie, D. (1947). *Austral. N.Z. J. Surg.*, **16,** 219.
Munro, D. (1945). *New Engl. J. Med.*, **232,** 149.
Ober, F. R. (1935). *J. Amer. med. Ass.*, **104,** 1580.
O'Connell, J. E. A. (1943). *Brit. J. Surg.*, **30,** 315.
Poppen, J. L. (1945). *New Engl. J. Med.*, **232,** 211.
Putti, V. (1927). *Lancet*, **2,** 53.
Rabinovitch, I. (1947). (Personal communication.)
Roofe, P. G. (1940). *Arch. Neurol. Psychiat.*, **44,** 100.
Weiss, P. (1943). *Anat. Rec.*, **86,** 491.
Wilson, S. A. K. (1940). "Neurology." London.

THE NEUROPATHOLOGICAL ASPECTS OF THROMBOCYTIC ACROANGIOTHROMBOSIS

A CLINICO-ANATOMICAL STUDY OF GENERALIZED PLATELET THROMBOSIS

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During the past two years we have been able to study the neuropathological changes in four patients in whom the principal symptomatology was fever, purpura, thrombocytopenia, and anæmia. In each instance the onset of symptoms was acute, the course of the illness rapidly progressive, and the termination fatal in a few days to weeks. The outstanding morphological finding was an increased cellularity and thrombosis of arterioles and capillaries in many organs, including the brain, by what are presumed to be agglutinated masses of platelets. In this respect it differs from the better known thrombocytopenic purpura of Werlhof and, as far as we know, from other diseases.

In our cases and in all of those which have hitherto been reported (see Table), neurological symptoms such as muscular weakness, hemiplegia, convulsions, drowsiness, confusion, stupor, or coma became manifest at some time, usually in the later stages of the illness. For this reason, and also because the neuropathological changes in a series of cases have not been described in detail, it was deemed advisable to bring this unusual syndrome to the attention of neurologists and neuropathologists.

This disease entity, if it be such, was first described in 1925 by Moschowitz. He had examined the organs of an adolescent girl who had succumbed to an acute febrile illness with joint pains, anæmia, petechial hæmorrhages in the skin, left hemiplegia, coma, and death within two weeks. In many of the capillaries and arterioles of the heart, liver, kidneys, and spleen there were thrombi of the "hyalin" type. Unfortunately a platelet count was not done. The brain was not examined.

In 1936 Baehr and others summarized the findings in four similar cases, each characterized by fever, progressive anæmia, mild icterus, and purpura. There were leucocytosis, reticulocytosis, and marked thrombocytopenia. Neurological symptoms consisting of convulsions, hemiplegia, delirium, or coma were present in three of the four cases. Necropsy revealed diffuse arteriolar and capillary thrombosis. The thrombotic material was believed to be composed of platelets.

Since the paper by Baehr and others nine other cases (Gitlow and Goldmark, 1939; Altschule, 1942; Bernheim, 1943; Trobaugh and others, 1946; Engel and others, 1947; Fitzgerald and others, 1947) have been reported, bringing the total to fourteen. All have shown platelet thrombi in the arterioles and capillaries, anæmia and thrombocytopenia. All have ended fatally within a few days to weeks. Four of the fourteen cases have been adult males and the rest adult females. The brain was examined in eight of these cases. Grossly the only changes were a few petechial hæmorrhages, and these were not demonstrable in all the cases. Bernheim was the first to report the brain lesions in detail. In addition to platelet thrombi she noted small foci of ischæmic necrosis. Engel and others have described vascular and parenchymal lesions in a further case which differed from others in that the illness lasted three months, occurring in two phases separated by an interval of three weeks. However,

some of the symptomatology in the first stages may have been due to a verrucous endocarditis with brain embolism.

The present communication summarizes the neuropathological findings in four cases which have been examined at the Mallory Institute of Pathology and the Neuropathology Laboratory of Boston City Hospital. One of our cases was reported by Trobaugh and others in 1946, and three others were described along with a general review of the subject in the paper of Fitzgerald and others in 1947.

Summary of Cases

Case 1. (Case II of Fitzgerald and others, 1947).—The patient was a 24-year-old negress who was brought to the hospital because of deepening coma of twelve hours' duration. She had had many illnesses during the previous three years. In 1942 she had had gonorrhœa and toxemia of pregnancy, and was delivered of a full-term stillborn infant. In 1945 she had an incomplete miscarriage. In the fall of 1945 she developed a skin rash after being given sulphonamide prophylactically during the extraction of abscessed teeth. In 1946 she was hospitalized for chest and joint pains and urticaria which were diagnosed as rheumatic fever. The urticaria continued intermittently and was being treated with benadryl when she first complained of faintness, suffocation, nausea, hæmatemesis, epistaxis, and menorrhagia about one week before admission. In the following days she became very weak and stuporous, and then, a few hours before entry, comatose.

Physical examination upon final admission showed a poorly nourished woman whose blood pressure was 98 mm. Hg systolic and 76 diastolic, pulse 90, respiration 30, and temperature 97° F. There was a macular rash over the skin of the chest, abdomen, back, and thighs. The pupils were equal in size but reacted sluggishly to light. The knee jerks were absent and the other tendon reflexes were one plus and equal. There were no other abnormal neurological signs.

The red cell count was 2.74 million per c.mm. of blood, hæmoglobin 7 g. and white blood cells 14,900 with 50 per cent. neutrophilic leucocytes, 46 per cent. lymphocytes, and 4 per cent. monocytes. The icteric index was 25. The blood sugar, non-protein nitrogen, and chloride values were normal. The CO_2 combining power was 35 vol. per cent. The cerebrospinal fluid was normal.

The patient remained in coma and died six hours after entry to the hospital, about a week or less after the onset of acute symptoms.

ANATOMICAL DIAGNOSIS.—There were arteriolar, capillary, and venular thrombi with minimal endothelial proliferation in the œsophagus, lungs, heart, liver, pancreas, spleen, kidneys, ovaries, uterus, vagina, lymph nodes, bone marrow, and brain; focal necroses of the myocardium, pancreas, and brain; multi-nucleated giant cells in the lung capillaries; extramedullary myelopoiesis of the spleen; hyperplasia of the vertebral marrow; petechiæ and ecchymoses of the heart and kidney; healed pleuritis of the left apex; and splenomegaly.

NEUROPATHOLOGICAL FINDINGS.—The brain was of normal size and configuration. There were no gross lesions in the cerebrum or brain stem.

Microscopic examination disclosed both vascular and parenchymatous changes in the cerebrum and brain stem as well as other changes of lesser significance.

The leptomeninges were thickened by an increased amount of relatively acellular collagenous connective tissue which in some places, particularly near the bottom of the sulci, contained small numbers of lymphocytes. The meningeal arteries and veins were normal.

There was an increased number of glia-cells in the marginal layer of the cerebral cortex, most marked in the sulci. They consisted of small clusters of astrocyte nuclei, some with visible perikaryon (amœboid cells), and scattered, elongated, microglial cells with irregular bipolar processes.

In all the parts of the cerebral cortex which were examined, that is, the hippocampus, premotor, sensorimotor, temporal, parietal, and occipital lobes, and in the caudate nucleus, putamen, thalamus, and substantia innominata, there was an increased cellularity of the arterioles, capillaries, and possibly small veins and thrombi of amorphous material partially or completely filling the lumen of many of these vessels. The adventitial cells of the aforementioned vessels were pale and swollen, and small granules of pigment, appearing yellowish in thionine-stained sections (probably "lipofuscin") could be seen in their cytoplasm. The endothelial cells of these vessels were increased in number and in size. Not infrequently the proliferating endothelial cells crowded concentrically into the lumen or extended diagonally or transversely across it. The thrombotic material which filled many of the vessels was finely granular and sometimes mixed with a few red corpuscles and white blood cells. In thionine stains the thrombotic mass was greyish and contained some minute chromatin particles and in hæmatoxylin and eosin stains it had a pink colour. One or two mast cells lay outside the adventitia of some vessels (Fig. 5 B).

In the tissue adjacent to many of the affected vessels in a small zone approximately 100 microns in size the nerve cells were pale with loss of Nissl substance and nuclear chromatin. In some of these minute foci several pleomorphic microglial cells * were found. In sections stained for myelin by Loyez technique there was no demonstrable change in the myelinated fibres. A few petechial hæmorrhages of well-preserved red corpuscles were also present in the cerebral cortex.

No significant changes could be demonstrated in the cerebellum or in sympathetic ganglia. The medulla, pons, and midbrain were not available for microscopic examination.

The arteries and veins, though occasionally surrounded by a few lymphocytes, macrophages with "lipofuscin" pigment and mast cells, showed no endothelial reaction or thrombi.

* We are referring, by this term, to microglial cells which are enlarged and have visible cytoplasm and processes and elongated or irregular nuclei.

NEURO-ANATOMICAL FINDINGS.—Multiple small vessels with endothelial reaction and thrombi; a few petechial hæmorrhages; multiple small foci of perivascular necrosis, some with microglia reaction; hyperplasia of glia-cells in the first cortical layer; fibrotic thickening of leptomeninges.

COMMENT.—The neuropathological changes which could be related to the acute disease process were the cellular proliferation in the walls of the arterioles and capillaries, the thrombi, the multiple small foci of nerve-cell alteration, and the scattered petechial hæmorrhages. The age of the glia-cell reaction in the marginal layer of cerebral cortex was difficult to judge. Unquestionably some of these glial changes and certainly the fibrotic thickening of the meninges were much older than the disease process under consideration.

The vascular and parenchymal lesions in the brain were of the same type as those in many of the other organs but differed from those in the heart by being less hæmorrhagic. Some of the cerebral changes may have been several days, possibly a week old, which was soon after the time of the onset of the hæmorrhagic diathesis; but most of them seemed to be more recent, corresponding more nearly to the development of stupor and coma.

Case 2 (Reported by Trobaugh and others, 1946).—The patient was a 24-year-old white man who had been well until two weeks before admission when he developed a cold with fever, prostration, and cough. His condition improved slightly in the next ten days, and on the eleventh day he felt generally ill and noticed hæmaturia. Severe vomiting of several hours' duration preceded entry to the hospital.

At the time of arrival to the hospital his temperature was 101° F., blood pressure was 120 mm. Hg systolic and 70 diastolic, and the pulse was rapid. He was restless and stuporous. His skin was pale and slightly jaundiced, with petechiæ over the abdomen, lower legs, and in the mouth and conjunctivæ. There were no other abnormal physical findings.

The hæmoglobin was 36 per cent., red cell count 2·18 million per c.mm. of blood, white blood cells 9,200. The differential count of white blood cells was 37 per cent. segmented neutrophilic leucocytes and 17 per cent. band forms, 23 per cent. lymphocytes, 17 per cent. monocytes, 4 per cent. eosinophils, 2 per cent. basophils, and 1 per cent. blast forms. Reticulocytes made up 10 per cent. of the red blood cells. The osmotic fragility test gave normal results and there were no cold agglutinins. Platelets were markedly reduced in stained smears of the blood. The icteric index was 20.

The patient became more deeply confused and restless and died on the third day in the hospital, the seventeenth day of the illness or six days after the onset of the hæmorrhagic diathesis.

ANATOMICAL DIAGNOSIS.—There were widespread arteriolar and capillary thromboses in the heart (myocardium), liver, pancreas, kidneys, adrenal cortex (mostly glomerular zone), ileum, and duodenum (mucosa), lymph nodes, bone marrow, and brain; small foci of necrosis, both anæmic and hæmorrhagic, in the myocardium, adrenal cortex (fasciculate zone) and pancreas; petechial hæmorrhages in the heart (epicardium, myocardium, and endocardium), lungs, and intestinal mucosa; multinucleated giant cells in the lung capillaries; hæmolytic icterus as evidenced by moderate hæmosiderosis of the liver and spleen and by hyperactive bone marrow; and bronchopneumonia.

NEUROPATHOLOGICAL FINDINGS.—No gross abnormalities of the brain were detected.

In microscopic sections of the cerebral cortex the leptomeninges appeared thickened owing to an increased amount of connective tissue. A few lymphocytes and an occasional neutrophilic leucocyte were seen in the pia. One small flat subarachnoid hæmorrhage of well-preserved red corpuscles was present. Some of the subarachnoid arteries were filled with blood cells, and in many of them minute granules of red colour in aniline-blue-stained sections were found on the endothelial surface and between the red corpuscles within the vessel lumen. In one medium-sized artery the endothelial cells were larger and more numerous than usual. No thrombi could be found.

In the marginal layer of the cerebral cortex, especially near the bottom of the sulci, there were clusters of astrocyte nuclei and single hypertrophied astrocytes with visible cytoplasm and pleomorphic microglial cells.

Throughout the cerebral cortex arterioles and capillaries of pronounced cellularity were noted. The endothelial cells were increased in number and had a pale, indented nucleus and a basophilic or even metachromatic cytoplasm in thionine-stained sections. These cells were arranged circularly or they protruded into the lumen, in some places appearing almost to occlude it. Smaller, more elongated cells with darker nuclei were found outside the endothelial cells. An occasional mitotic figure could be seen in an endothelial cell. There were a few lymphocytes and an occasional unidentified mononuclear cell or neutrophilic leucocyte in the wall of the vessel or its perivascular space. The external diameter of these vessels was larger than normal. The lumen of many vessels was partly or completely filled with a granular amorphous material similar to that in Case 1.

There were only slight parenchymal changes consisting of a small zone around the most severely affected vessels where the nerve cells were pale, that is, loss of Nissl substance and pale nuclei, or, less often, had disappeared. In some of these foci microglial cells had increased in number and were pleomorphic. A few small hæmorrhages were found in the cerebral cortex.

These vascular and parenchymatous changes were present in all parts of the cerebral cortex, being most conspicuous in layers II, III, and IV. Similar vascular lesions were seen in the medulla, and in fact the tissue damage was much more pronounced here than in the cortex. These medullary lesions took the form of small foci of necrosis and hæmorrhage in which there were clumps of swollen astrocytes and pleomorphic microglial cells. Such lesions were situated in the lateral part of the magno-cellular reticular formation and nucleus of Burdach (Fig. 5A). In addition to the focal lesions, all the nuclei appeared to contain a few scattered swollen astrocytes and microglial cells.

NEURO-ANATOMICAL FINDINGS.—There were multiple small vessels with endothelial proliferation and thrombi; a few petechial hæmorrhages in the cerebral cortex and subarachnoid space; endothelial reaction in one medium-sized leptomeningeal artery; infiltration of leptomeninges by a few lymphocytes and an occasional neutrophilic leucocyte; multiple small foci of necrosis in the cerebral cortex and in the nuclei of the medulla—some, particularly in the medulla, with glia-cell reaction; and diffuse glia-cell proliferation in the medulla and first cortical layer.

COMMENT.—In this case it was concluded that the alteration of the walls of the arterioles and capillaries, the thrombi, the perivascular tissue changes, and the petechial hæmorrhages were the underlying pathology of the disease under consideration. The significance of meningeal fibrosis and glia-cell reaction in the marginal layer of cerebral cortex and in some parts of the medulla could not be determined.

The vascular lesions in the brain were exactly like those in other organs. Many of the parenchymatous changes were of such a character as to be adjudged about a week old. Presumably the vessels in all the different organs had been involved at about the time of, or slightly before, the hæmorrhagic tendency became manifest. The vascular changes in the brain were apparently slightly older and somewhat more advanced in this case than in Case 1.

Case 3 (Case I of Fitzgerald and others, 1947).—The patient was a 34-year-old white male who had been well until three weeks before admission, when he first experienced slight nausea and severe epigastric pain. He continued to work for the next three weeks until weakness, fatigue, anorexia, and constipation necessitated entry into the hospital for examination. In the past the patient had had an obscure abdominal disorder for which he took bismuth and aluminium hydroxide. There was no history of exposure to other drugs or toxic agents or of allergy.

The patient was restless and apprehensive. His temperature, pulse, respiration, and blood pressure were within normal limits. The skin was pale and dry. There were numerous recent retinal hæmorrhages. The remainder of the examination was not remarkable.

The red cell count was 2·14 million per c.mm. of blood, and the hæmoglobin was 42 per cent.; the white cell count was 13,700, with 60 per cent. neutrophilic leucocytes, 10 per cent. band forms, 1 per cent. juvenile forms, 1 per cent. myelocytes, 27 per cent. lymphocytes, and 1 per cent. monocytes. The platelet count was 88,000; the clotting time was 3 minutes, and the bleeding time 11·5 minutes. The prothrombin time was considerably prolonged in comparison to a normal control. The osmotic fragility of the red corpuscles was normal. The icteric index was 13.

His temperature varied from 99 to 102° F. but was normal after the sixth hospital day. The patient was very restless and often confused. He complained of dizziness. On the twelfth hospital day he became comatose and died a few hours later, twelve days after the exacerbation of the disease and five weeks from the onset of his illness.

ANATOMICAL DIAGNOSIS.—There was diffuse arteriolar, capillary, and venular thrombosis with endothelial proliferation in the heart, lungs, liver, spleen, adrenals, gastrointestinal tract, kidneys, prostate, testicles, lymph nodes, bone marrow, brain, and spinal cord; petechial hæmorrhages and ecchymoses in the skin, pericardium, myocardium, lungs, peritoneum, small intestines, and brain; multiple foci of necrosis in the myocardium and brain; multinucleated giant cells in the capillaries of the lung; cardiomegaly, hepatomegaly, and splenomegaly; hyperplasia of the bone marrow; tracheobronchitis and bronchopneumonia; atelectasis; and interstitial cell hyperplasia of the testicles.

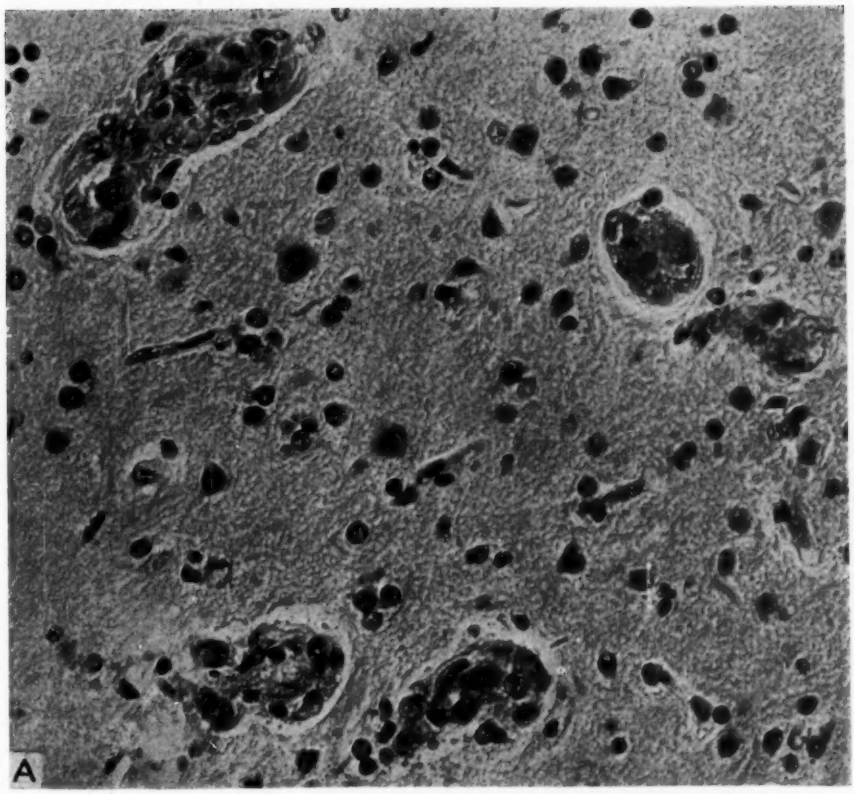
NEUROPATHOLOGICAL FINDINGS.—The only gross abnormality in the brain was the presence of petechial hæmorrhages. They were fifteen to twenty in number and could be seen on the cut surface of the cerebral cortex, lenticular nucleus, thalamus, superior colliculi, pontine nuclei, and cerebellar cortex.

In microscopic sections the leptomeninges were normal except for a few scattered lymphocytes and an occasional neutrophilic leucocyte. The large arteries showed slight reduplication of the internal elastic lamina and irregular basophilic staining of parts of the media. In the walls of some middle-sized arteries there were irregular "calcified" bodies situated chiefly in the media and sometimes in the intima and adventitia.

In some parts of the grey matter there was cellular proliferation and partial or complete thrombosis of most of the arterioles and capillaries (Fig. 1 A and B). The endothelial cells were increased in number, had pale and enlarged nuclei which protruded into the lumen and encircled or invaded thrombi of granular character (Fig. 2 C). The cytoplasm of some of these cells was quite basophilic and contained small dark granules. No definite mitotic figures were found. In a few vessels the cellular reaction was not accompanied by thrombosis. In some of the vessels, stained for reticulum, silver-impregnated fibrils often ending in bulbs were found between the intimal and adventitial cells of the vessel wall (Fig. 2 A and B). In van Gieson-stained sections a slight trace of reddish colour but no fully developed fuchsinophilia of the intercellular fibrils could be seen. In the choroid plexus were some vessels with a pronounced cellular reaction nearly completely obliterating the lumen (Fig. 5 C).

Parenchymatous lesions were found in the cortex of the frontal, parietal, temporal lobes and the thalamus, midbrain, pons, and medulla but they varied greatly in different regions. In the cerebral cortex the vessels with reactive changes were surrounded by a zone in which nerve cells were poorly stained. The nerve-cell alteration was more pronounced in the sensori-motor cortex, where in some foci these cells had completely disappeared or were shrunken, homogeneous, and pale, with a darkly stained nucleus. Many swollen astrocyte nuclei and pleomorphic microglial cells were found in some of these foci. There were also several collections of extravasated red corpuscles. In the marginal layer of the cortex, small clusters of naked astrocyte nuclei and scattered "ameboid" astrocytes were found.

The most severe lesions were in the superior colliculi



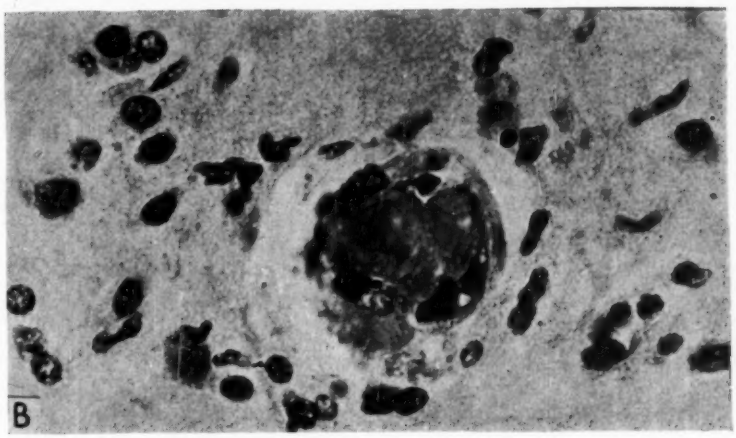


FIG. 1.—A. Cortical vessels with granular thrombi and cellular reaction of the wall. Case 3. Giemsa stain. Magnification x approx. 400.

B. Cortical vessel with thrombus and increased number of endothelial cells, growing inwards at the indentation of the thrombus. Mobilization of pleomorphic microglia in tissues. Case 3. Giemsa stain. Magnification x approx. 600.

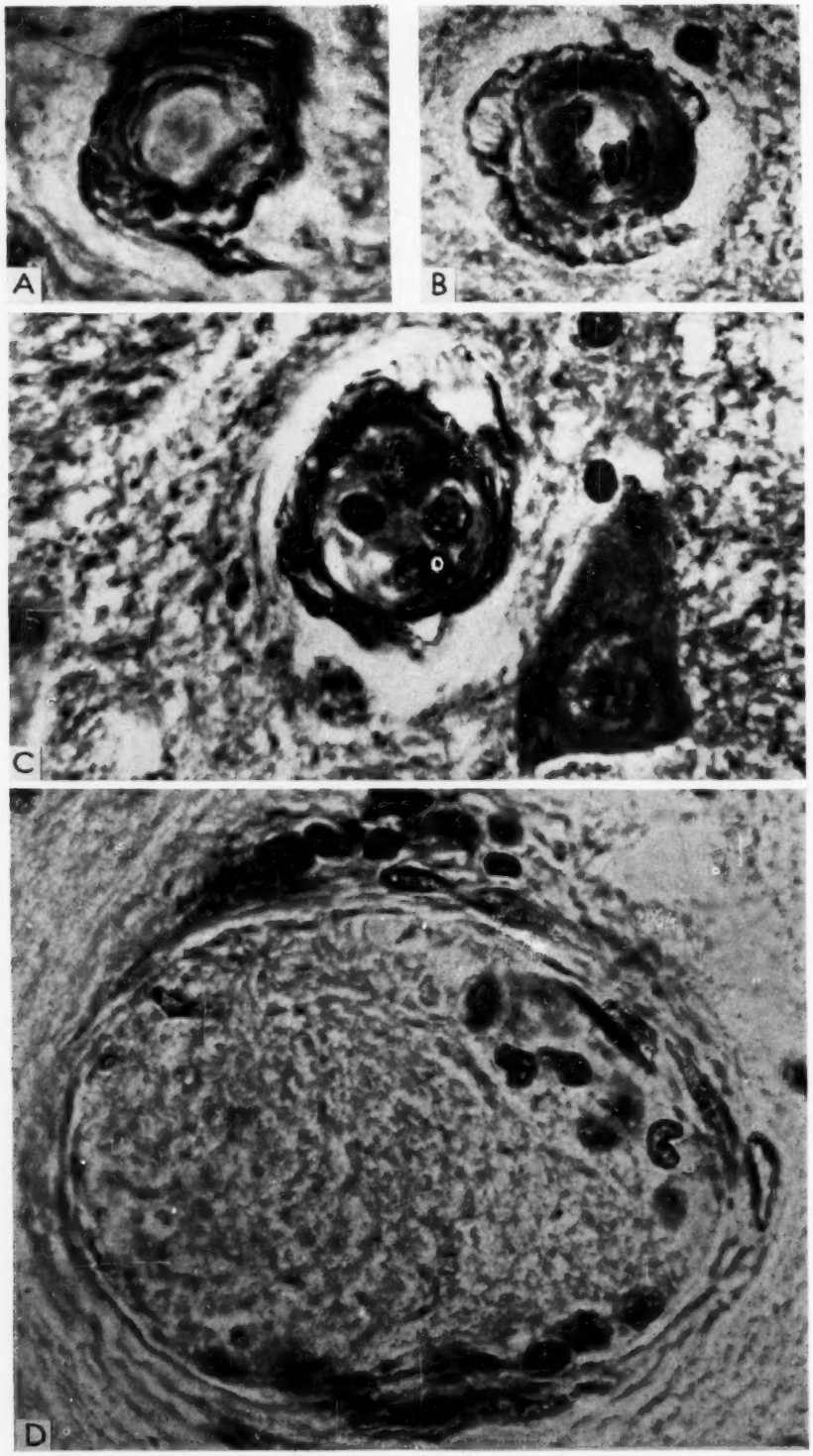


FIG. 2.—A. Small artery of medulla with thick wall with an increased number of cells, argentophil fibrils, and some lymphocytes. The lumen is filled with red blood corpuscles. Case 3. Silver reticulum stain. Magnification x 1,800.

B. Small artery of medulla with cellular reaction of intima and argentophil; adventitial fibrils. The lumen is partly occluded by granular mass, the black irregular material in the lower half. Case 3. Silver reticulum stain. Magnification x 1,800.

C. Small artery of hypoglossal nucleus with proliferated intimal cells filling the lumen. Normal nerve cell and oligodendrocytes to the right. Case 3. Silver reticulum stain. Magnification x 1,800.

D. Small vein in the substantia innominata. Greyish coloured granular masses filling the lumen except for a segment in the upper right where there are a few white and red blood corpuscles. Above is a perivascular collection of lymphocytes. There is almost no cellular reaction in the wall of the vessel. Case 4. Thionine stain. Magnification x 1,800.

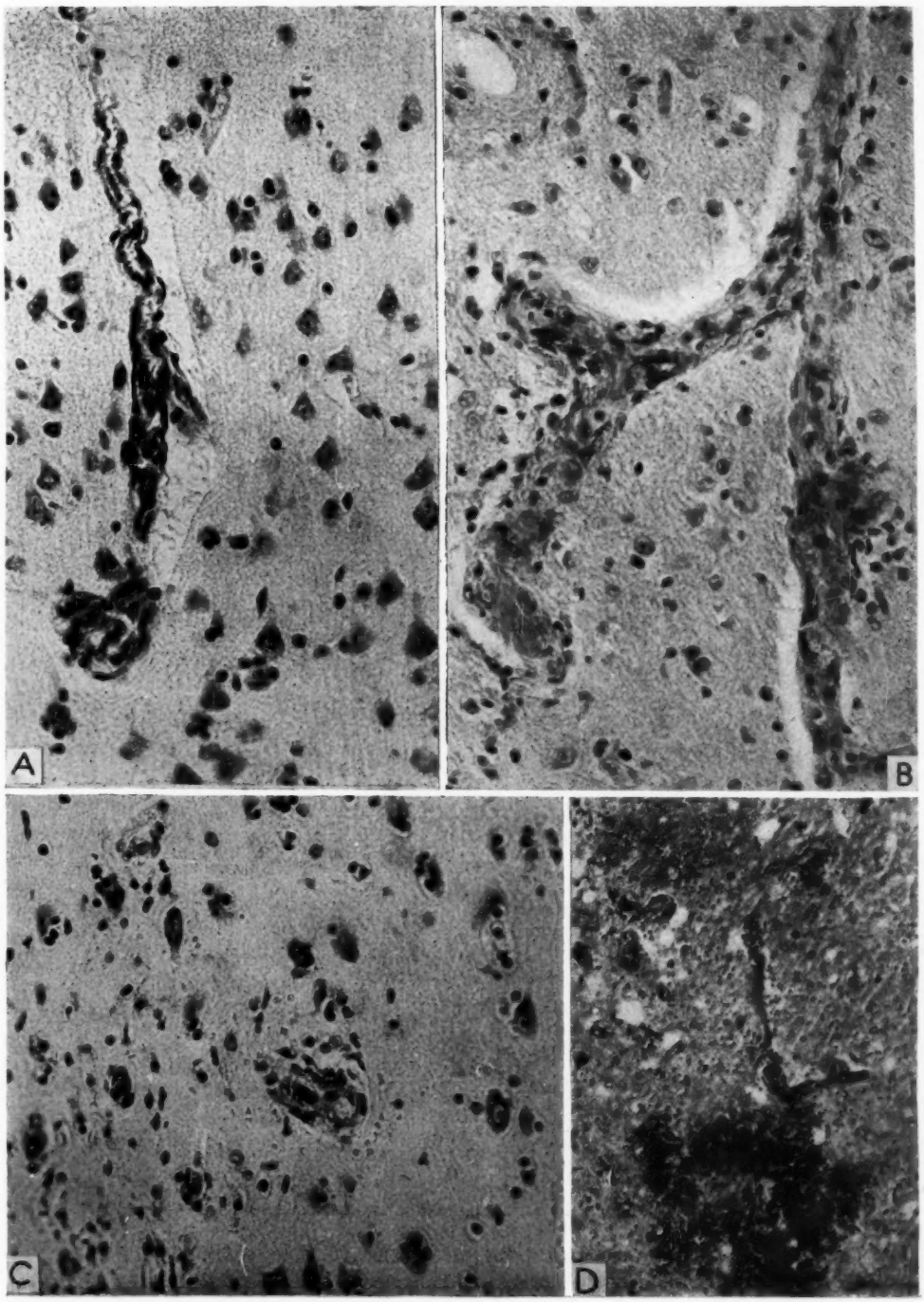


FIG. 3.—A. Cortical vessel showing cellular reaction of the wall from the point of bifurcation and downwards. The nerve cells mostly to the right of the vessel are very pale but without characteristic pathological alterations. Case 4. Thionine stain. Magnification x 200.

B. Radiating vessel from the superior colliculus. Note that the vascular reaction extends for a short distance above the point of bifurcation and downwards along both branches. At the tip of the left branch the lumen is filled with a granular thrombus. Case 3. Hæmatoxylin and eosin stain. Magnification x 200.

C. Note increased number of elongated microglia to left of a small thrombosed vessel with cellular reaction of the wall. From the gyrus hippocampi. Case 4. Thionine stain. Magnification x 200.

D. Thrombosed vessels in the centre with hæmorrhages at the periphery above and below, the latter one a " ring " hæmorrhage with central necrosis. From the superior colliculus. Case 3. Hæmatoxylin and eosin stain. Magnification x 100.

FIG. 4.—A. Thrombosed vessels with cellular wall surrounded by a narrow zone with altered myelin sheaths. From the mesencephalon. Case 4. Loyez stain. Magnification x 100.

B. High-power view of the group of vessels to the left in A, showing myelinated fibres around a few of the vessels. Loyez stain. Magnification x 340.

C. High-power view of the vessel to the right in A, with a broad zone of non-impregnable myelin sheaths. Loyez stain. Magnification x 340.

D. Rounded focus of ischæmic necrosis with partial destruction of myelinated fibres between several damaged vessels. From mesencephalon. Case 4. Loyez stain. Magnification x 100.

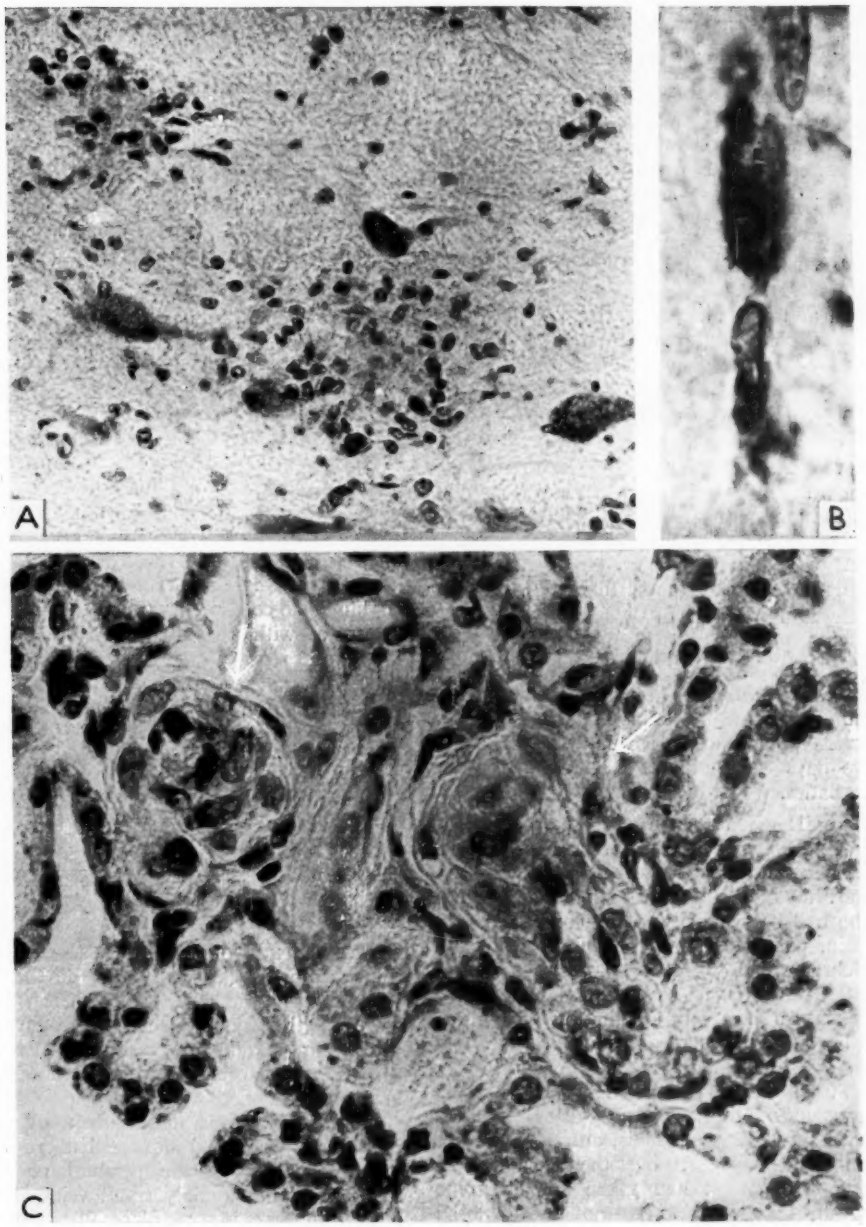


FIG. 5.—A. Minute pericapillary (?) necrosis with surrounding hypertrophied astrocytes and microglia from the cuneate nucleus. Case 2. Thionine stain. Magnification x 200.

B. Mast cell adhering to the surface of a small vessel, the intimal cells of which are seen in the midline of the figure. To the right is the lumen of the vessel and to the left the brain tissue. Case 1. Thionine stain. Magnification x 1,800.

C. Choroid plexus. Arrows point to vessels showing cellular proliferation and obliteration of their lumens. Case 3. Thionine stain. Magnification x 800.

and tegmentum of the midbrain. The vessels passing from the surface of the colliculi towards the aqueduct were conspicuous on account of their cellularity and the thrombi. One of them, an arteriole which was cut in longitudinal section, contained a thrombus in one portion on either side of which were normally coloured red corpuscles (Fig. 3 B). Swollen astrocytes and pleomorphic microglial cells were present in the tissue adjacent to the thrombus. There were several fresh perivascular and "ring" hæmorrhages (Fig. 3 D), and in some few places microglial cells were filled with hæmosiderin. There was quite extensive nerve-cell destruction in these areas.

In the pons and medulla practically all the nuclei showed vascular changes, focal nerve cell loss, and clumps of astrocytes and pleomorphic microglial cells. Similar changes were found in the upper part of the cervical spinal cord and at the level of the decussation of the pyramidal tracts.

NEURO-ANATOMICAL FINDINGS.—There were multiple small vessels with endothelial proliferation; cellular endothelial reaction and thrombi; multiple small perivascular foci of altered nerve cells; multiple small, recent and older hæmorrhages, especially in the colliculi; and diffuse glia-cell reaction in the first cortical layer.

COMMENT.—The vascular and parenchymatous lesions were of the same type as in Cases 1 and 2 but were considerably older as judged by the increase in reticular connective tissue and in one lesion many microglial phagocytes containing hæmosiderin. The latter represents a reaction to hæmorrhage that was probably ten to twelve days old and correlates well with the clinical exacerbation which occurred at that time.

Case 4 (Case III of Fitzgerald and others, 1947).—The patient was a 28-year-old white man who had had rheumatic fever at the age of 12 years and had been rejected by the army in 1941 because of cardiac murmurs. Since 1943 he had been subject to frequent attacks of precordial pain, palpitation, and occasionally fainting spells. In February, 1947, five weeks before admission to the hospital, he began to have mild pains in both knees; there was no redness or swelling of these joints. Four weeks later he had fever and chills, cough, and back pain. A dull, generalized headache began shortly afterwards. Sulphadiazene was given two days before entry to the hospital. On the following day he vomited clotted blood, had a severe epistaxis, and voided urine of red colour. A rash appeared over the face and neck.

Once before the patient had taken sulphadiazene without untoward reaction. He had not been exposed to other toxic drugs, such as benzene, inorganic solvents, or fava beans.

EXAMINATION.—The temperature was 99° F., the pulse 88, the respiration 20, and the blood pressure 114 mm. Hg systolic and 76 diastolic. The patient was lethargic, but when aroused responded appropriately to questions. There were petechial hæmorrhages in the skin over the face, and in the oral mucous membranes and conjunctivæ. The cervical, axillary, and inguinal lymph nodes were slightly enlarged. The heart was of normal size and the rhythm was regular but there were apical systolic and diastolic murmurs and an aortic systolic murmur. The liver and spleen were not palpable. No abnormal neurological signs were present.

LABORATORY DATA.—The urine was normal. The hæmoglobin was 7 g., the red cell count 2·3 million per 100 c.mm. of blood, the white cell count 11,650 with 86 per cent. neutrophils, 11 per cent. lymphocytes, and 3 per cent. monocytes. The hæmatocrit was 17. The bleeding and clotting times were normal. The platelets numbered less than 50,000. The blood culture was negative. The electrocardiogram was normal.

COURSE IN HOSPITAL.—The patient remained drowsy until the fourth hospital day, when he was seized with several generalized convulsions during which the head and eyes turned to the left. He was confused for several hours after the seizures, and during this time his temperature rose to 103° F. Penicillin was given in a dosage of 100,000 units every three hours. On the eighth hospital day he went into status epilepticus which could be controlled only by large doses of paraldehyde, given intramuscularly. Following this the patient remained comatose. No other abnormal neurological findings were noted. His cerebrospinal fluid was under a pressure of 110 mm., was clear and colourless, and contained no cells and a protein of only 26 mg. He was transfused with whole blood several times and his red cell count rose to 3·5 million. However, the coma persisted and he died on the twelfth day in hospital, or thirteen days after the first symptoms of hæmorrhagic diathesis.

ANATOMICAL DIAGNOSIS.—There were multiple thrombi in the arterioles, capillaries, and venules in the heart, kidney, bone marrow, and brain; petechial hæmorrhages in the heart and brain; multiple foci of necrosis in the heart and brain; multinucleated giant cells in the capillaries of the lung; hyperplasia of the bone marrow; and diffuse myocardial fibrosis of moderate degree.

NEUROPATHOLOGICAL FINDINGS.—Three or four petechial hæmorrhages were visible on the surface of the cerebral and cerebellar hemispheres, and about 20 more in the form of discrete round hæmorrhages, 1 to 2 mm. in diameter, were seen in the cortex, basal ganglia, and substantia nigra when the formalin-fixed brain was sectioned.

There were moderate numbers of astrocytes with visible cytoplasm and elongated microglial cells in the marginal layers of the cerebral cortex. Arterioles, capillaries, and possibly small veins were exceedingly cellular and were in some places filled with red corpuscles and white blood cells and in others occluded by homogeneous or slightly granular masses.

The cells in the vessel walls had an elongated, thin cytoplasmic body and were arranged concentrically around the lumen. The most centrally placed cells had large multiformed nuclei and more abundant cytoplasm. Both the endothelial and adventitial cells appeared to have undergone hyperplasia. Sometimes the thrombus had retracted from the vessel wall, and the detached surface was covered by a thin basophilic process of an endothelial cell. In places where an arteriole was

fortuitously cut in longitudinal section the mural cellularity and thrombosis could be traced past a bifurcation of the vessel into capillaries for a short distance (Fig. 3 A). Basophilic granules were seen in the cytoplasm of some cells of the vessel wall. An occasional mitotic figure was found. A few lymphocytes, mononuclear cells, and neutrophilic leucocytes had infiltrated the wall or the perivascular space of the affected vessels.

Some of the nerve cells and glia-cell nuclei immediately adjacent to the affected vessels were pale or in some places the neurones had disappeared. There were a few swollen astrocyte nuclei in some of these foci, and in one of them many pleomorphic microglial cells as well (Fig. 3 C). In rare instances damaged blood vessels were surrounded by " ring " hæmorrhages. The nerve cells were preserved in Sommer's sector of Ammon's horn.

A Loyez-stained section from the mesencephalon demonstrated the loss of a few myelinated fibres next to the most severely damaged vessels (Fig. 4 A, B, and C).

The vascular lesions were quite pronounced in the putamen and less so in the globus pallidus, thalamus, caudate nucleus, paraventricular hypothalamic nucleus, and substantia innominata (Fig. 2 D), in the substantia nigra, the abducens, inferior olivary, and magnocellular part of the lateral reticular nuclei, and the superior cerebellar peduncle and dentate nucleus. In the brain stem there was a slight diffuse increase in astrocytes and microglial cells and also several minute foci of swollen astrocytes and pleomorphic microglial cells. In the walls of many of the arteries in the pallidum there was a deposition of basophilic material; some of these vessels also showed cellular hyperplasia and thrombosis. In one focus in the dorsal part of the superior cerebellar peduncle all the vessels were damaged in a quite large area (Fig. 4 A, B, C), and the intervening nerve and glia cells were shrunken and pyknotic, while the myelinated fibres were damaged (Fig. 4 D).

In the choroid plexus of the lateral ventricles there were a few arterioles or small arteries which showed a slight but definite cellular hyperplasia. At the base of the brain a few meningeal arteries showed a slight proliferation of endothelial cells but no other changes. The subependymal glia had multiplied focally near the fourth ventricle, the aqueduct of Sylvius, and the lateral ventricle.

NEURO-ANATOMICAL FINDINGS—There were multiple small vessels with endothelial proliferation and platelet thrombi; multiple small perivascular foci of partial or complete necrosis in the cerebral cortex and brain stem; several old foci of ischæmic necrosis in the cerebral cortex; diffuse glia-cell hyperplasia in first cortical layer, subependymal zone, and brain-stem nuclei; and a few petechial hæmorrhages.

COMMENT.—All the damaged vessels in the brain did not show the same degree of reaction; some of them exhibited only a markedly increased cellularity, and others were partly or completely occluded by thrombi without any cellular reaction. In comparison to the myocardial lesions there was in the brain a more pronounced cellular reaction and considerably fewer hæmorrhages. Some of the lesions in the brain were mild and acute, whereas others, in which a definite glial reaction was demonstrable, must have been of one or two weeks' duration. Presumably these older lesions coincided approximately with the progression of symptoms thirteen days before the patient's death.

Discussion

Symptomatology.—Although subject to considerable variation, the clinical picture of this disease, as formulated from all of the published cases, tended to follow a recognizable pattern. Usually it presented three main features: the signs of hæmorrhagic disease, severe anæmia, and neurological symptoms.

Both sexes were affected, female more often than male. The disease was somewhat more common in adolescents and young adults and occurred in both white and coloured races.

Some of the patients had enjoyed excellent health before the onset, whereas others had suffered from rheumatic fever, urticaria, or a recent upper respiratory infection. Several of them had rather vague prodromal symptoms, such as nausea and vomiting, weakness, malaise, and abdominal pain. When first seen the patients were, as a rule, quite pale and complaining of weakness, lassitude, vague pains in their joints, abdomen, or in other parts, or fever and chills. Usually small hæmorrhages in the form of purpura, epistaxis, hæmatemesis, hæmaturia, or menorrhagia had already occurred. Quite soon the bleeding became more profuse, and fever, if not already present, appeared. Neurological symptoms most often developed at this stage of the disease but were occasionally present from the onset. For the most part they were cerebral in nature and consisted of confusion, coma, motor paralysis, and convulsions.

The onset of symptoms was usually acute and the course progressive with a fatal termination in from one to eight weeks.

The blood presented the appearance of moderately severe anæmia with red corpuscles ranging from 1·0 to 2·74 million per 100 c.mm. of blood. The hæmoglobin was low, usually giving a colour index of about 1·0. The white cell count was normal or elevated, with a neutrophilic leucocytosis. In stained films there was anisocytosis, polychromatophilia, and reticulocytosis. Occasionally a few nucleated red cells and myelocytes were present. Platelets were reduced in number, usually below 50,000. The Rumpel-Leede sign was present. Bleeding time was often prolonged, over 30 minutes in some cases; and, although clotting was usually not delayed, the coagulum retracted poorly. Erythrocyte fragility was normal. The icteric index ranged from 8 to 25 and the quantitative Van den

TABLE

SUMMARY OF CLINICAL FINDINGS IN THE 13 REPORTED CASES WITH THROMBOCYTIC ACROANGIOTHROMBOSIS

Case	Sex and colour	Age	General clinical findings	Neurological findings	Total duration of illness
1. Moschowitz, 1925	F,W	16	Weakness and joint pains and pallor, petechiæ, (?) jaundice	Left hemiparesis Kernig sign	14 days
2. Baehr, Klemperer, Schifrin, 1936	F,W	9·5	Listlessness, hæmaturia, pallor and skin purpura, retinal hæmorrhages, splenomegaly	None	7 weeks
3. Baehr, Klemperer, Schifrin, 1936	F,W	18	Weakness and pallor, icterus and petechial skin hæmorrhages	Headache, convulsions	2 months
4. Baehr, Klemperer, Schifrin, 1936	F,W	22	Urticaria, purpura, retinal hæmorrhages, nausea and vomiting	Delirium and stupor	9 days
5. Baehr, Klemperer, Schifrin, 1936	F,W	48	Upper respiratory infection, purpura, icterus, retinal hæmorrhages	Right hemiparesis, coma	2 weeks
6. Gitlow and Goldmark, 1939	F,W	18	Upper respiratory infection, purpura, enlargement of spleen and liver	Right hemiparesis, coma	18 days
7. Altshule, 1942	F,W	50	Malaise, pallor, hepatomegaly, and splenomegaly	Confusion, left facial weakness, delirium	13 days
8. Bernheim, 1943	F,W	33	Weakness, dermatitis, pallor, purpura	Left facial weakness, hemianæsthesia, convulsions	2 weeks
9. Trobaugh, Markowitz, Davison, and Crowley, 1946	M,W	24	Upper respiratory infection, icterus, and purpura	Restlessness, stupor, coma	15 days
10. Carter, 1947	M,C	66	None	Confusion, aphasia, unequal tendon reflexes, right Babinski, coma	12 days
11. Engel, Schemker, and Humphrey, 1947	F,C	15	Sore throat, fever, malaise, purpura, hæmaturia, menorrhagia, vomiting, ECG changes; improved.	Blurred vision, headache, delirium	50 days
			5 weeks later: recurrence of systemic and hæmorrhagic symptoms	Coma, deviation of head and eyes to right, left hemiparesis, right facial weakness, flaccid paraplegia	7 days
12. Fitzgerald, Auerbach, and Frame, 1947	M,W	24	Nausea, vomiting, abdominal pain, pallor, purpura	Restlessness, confusion, and coma	5 weeks
13. Fitzgerald, Auerbach, and Frame 1947	F,C	27	Urticaria, faintness, epistaxis, hæmatemesis, menorrhagia, pallor, hepatomegaly	Stupor, coma	1 week
14. Fitzgerald, Auerbach, and Frame, 1947	M,W	28	Rheumatic fever, precordial pain, syncope, joint pains, chills and fever, epistaxis, hæmatemesis, hæmaturia, pallor and purpura	Status epilepticus, confusion, coma	2 weeks

Bergh analyses from 0·5 to 2·5 mg. The cerebrospinal fluid was normal in the three cases in which it was examined.

As shown in the Table, twelve of the thirteen cases had neurological symptoms at some stage of the disease. Some alteration in the state of consciousness was most frequent. This was variously designated in the records as irrationality, restlessness, confusion, delirium, stupor, or coma. It usually began with confusion and progressed terminally to coma. The latter was a sign therefore of grave prognostic import ; once coma set in, death always followed within a few days.

Motor paralysis was observed in seven of the fourteen cases. The paralysis was not complete in any of them. In five of the seven there was a hemiparesis with involvement of face, arm, and leg, and diminished tendon and abdominal reflexes and a Babinski sign on the side of the weakness. In three cases a facial weakness was present, but from the meagre descriptions in the records one could not decide whether it was due to involvement of the facial nucleus or nerve or to a supranuclear lesion.

Seizures occurred in three cases. They were generalized in each instance, and in one case went on to status epilepticus which undoubtedly contributed to death. Focal or unilateral convulsions were not observed, which is rather surprising in view of the focal character of certain other neurological findings.

Less frequent findings were a left hemianæsthesia and deviation of the head and eyes to right as in Bernheim's case (1943) ; the latter finding was also present in the case of Engel and others (1947). In the case reported by Carter (1947) there was agrammatism, acoustic and verbal agnosia, and ideokinetic apraxia, but inasmuch as the patient was both confused and aphasic the validity of some of these interpretations of the mental state might be questioned.

Evidence of spinal cord or possibly peripheral nerve damage was observed in only three cases. The second of Fitzgerald's cases had nuchal rigidity and absent knee jerks, the case of Engel and others had a flaccid paraplegia, and in Carter's case there were at times hypoactive knee jerks, absent ankle jerks, diminished pain and touch sensation in the legs, and diminished temperature sensation in all four extremities but no motor weakness. As stated above, Carter's patient was confused and aphasic and some of the signs were probably not dependable.

Central Nervous System Lesions.—In the present material the outstanding neuropathological changes were (a) cellular hyperplasia, endothelial and probably adventitial, of arterioles, capillaries, and venules ; (b) thrombi of agglutinated platelets in arterioles, capillaries, and venules of cerebral cortex, basal ganglia, and brain-stem nuclei ; (c) foci of nerve cell damage and in places glial proliferation ; (d) petechial hæmorrhages.

The character of the vascular change has already been described in the case summaries. An excessive cellularity of the arterioles, capillaries, and venules and an increase in their total diameter were the most noticeable findings in hæmatoxylin-eosin and thionine stains (Fig. 1 A). It was not always possible to be sure of the exact identity of these cells. Those nearest the lumen had rather pale, indented nuclei and moderate amounts of basophilic cytoplasm and were abnormally oriented to the vessel, some encircling and narrowing the lumen and others traversing the lumen and dividing it. In Cases 2 and 4 a few mitotic figures were found. The outer cells in the vessel wall were more elongated, had more heavily chromatinized nuclei and, in Case 1, granules of lipofuscin in their cytoplasm. Occasionally a few lymphocytes, a neutrophilic leucocyte, or an unidentified mononuclear cell were interspersed between these cells. In silver stains for reticular connective tissue there was in some vessels a slight increase in argentophilic fibrils either separating the proliferating cells or extending outward from the adventitia. In van Gieson stains some of these fibres were faintly fuchsinophilic. All stages of vascular changes could be demonstrated in each individual case (Fig. 2 A, B, and C).

The arterioles, capillaries, and venules were occluded by thrombi which on differential staining appeared to be masses of agglutinated platelets. In the phosphotungstic acid hæmatoxylin stain the thrombi were a pale brown and no fibroglia were present. Weigert's stain for fibrin coloured the thrombi a dull grey, and in this and the phosphotungstic acid hæmatoxylin stain only an occasional bluish strand of fibrin was present. With Mallory's aniline blue stain the thrombi were a lavender colour and no fibrillar elements could be seen. In reticulum stains no argentophilic fibrils were seen within the thrombi. In Giemsa stain (Wolbach's modification) the thrombi were pale grey to blue. The earlier lesions stained a dark blue, older ones a greyish-blue, and no red colour was apparent in either. In the normal vessels between red corpuscles and leucocytes fine granules of about the size of normal platelets also stained a bluish colour. The van Gieson stain gave a pink colour to the thrombi, whereas the red blood corpuscles were yellow. No bacteria or inclusion bodies could be seen. Hæmoglobin stains showed the thrombi to be a red or brownish-red in contrast

to the olive green or green of the red blood corpuscles. From these studies it was concluded that the thrombi were composed of agglutinated platelets and not of erythrocytes, leucocytes, fibrin, hæmosiderin, or hæmoglobin. The failure of the platelets to appear as reddish bodies with bluish granules in the Giemsa stain does not disprove this possibility. Platelets often disintegrate so rapidly in post-mortem material that they cannot be identified by specific stains.

The blood vessels which were involved in this pathological process were the arterioles, capillaries, and possibly venules of the grey matter. In sections where the vessels could be followed for a distance in longitudinal section both the cellular reaction and the thromboses were restricted to a portion of the vessel extending for a short distance into the branching capillaries. In the cases of longer duration there was a tendency for larger veins to become thrombosed.

Cases 1 and 2 presented the "earliest" reaction and Cases 3 and 4 the "oldest" changes (see page 41). In the latter cases, however, it was possible to find vascular lesions of all different ages, indicating that the process had continued over the entire period of the illness. In Cases 2 and 4 one or two small arteries in the leptomeninges had been involved.

Damage to parenchyma, although present in every case, was slight. Alteration of some of the nerve cells in small foci around the thrombosed vessels was the usual finding. Even in the oldest lesions the change in the neurones was not commensurate with longstanding vascular occlusion (Fig. 3 A). The nerve cells had seldom undergone complete disintegration: they were usually faintly stained, with a pale bluish cytoplasm and nucleus. In some foci there were a few enlarged astrocytes and elongated or pleomorphic microglial cells. By Loyez myelin stains and Gros-Bielschowsky axis cylinder stain it has not been possible to demonstrate any massive destruction of myelinated fibres or axis cylinders next to the altered blood vessels, but there was some demyelination (Fig. 4 A, B, C). In the brain stem there were a few larger foci with necrosis of nervous tissue and a more marked glial reaction (Fig. 4 D, and Fig. 5 A).

Petechial hæmorrhages were found in all our four cases. They were easily visible to the naked eye in Case 4, and mistaken for congested blood vessels in Cases 2 and 3. In Cases 2 and 4 they were more numerous in the midbrain than elsewhere. They ranged in size from a fraction of a mm. to 2·0 mm., and at most numbered 25 or 30 in all*. Unlike some other types of brain purpura they were for the most part confined to the cortical grey matter, basal ganglia, and brain stem. Only a few were seen in white matter. In microscopic sections the hæmorrhages were discrete and of two types, perivascular, and ring-shaped around a necrotic centre. Usually they were in close relationship to damaged vessels. Sometimes an altered vessel or cluster of histiocytes were situated in the centre of a ring hæmorrhage. In older lesions there was a well-marked proliferation of pleomorphic microglial cells amongst which pale red corpuscles and swollen astrocytes were visible. Microglial phagocytes containing hæmosiderin pigment were noted in Case 3. Wherever the reaction of glial cells was intense, evidences of hæmorrhage could usually be found.

In the case in which the neurological symptoms were of briefest duration there were mast cells in the adventitia of the walls of damaged vessels (Fig. 5 B). This finding was of interest when viewed in the light of the recent discovery of Jorpes and others (1937), Holmgren (1940), and Sylven (1945), that the mast cell contains and secretes heparin. Conceivably they constituted in our case a reaction of the organism to thrombosis of small vessels. In the other three cases some of the outer cells in the vessel wall had a "basophilic," metachromatic, or slightly hyperchromatic cytoplasm in thionine-stained sections but no true mast cells were present. The exact nature and purpose of these cells could not be ascertained.

The distribution of the vascular and the parenchymal lesions were fairly uniform in each of the four cases. For the most part they occurred in grey matter and not the white. In the cerebral cortex the second to fourth layers were affected more than the others. Changes of the same type were found in the grey matter of the caudate and lenticular nuclei, the thalamus, hypothalamus, and subthalamus and nuclear structures of the midbrain, pons, and medulla and to a lesser degree the grey matter of the cerebellum. Definite vascular abnormalities were found in the vessels of the choroid plexus in two cases (Fig. 5 C) and questionably in subarachnoid, vessels of two cases.

It was difficult to determine the age of the vascular changes because, as this is a new type of pathologic reaction, one dare not use as a standard of comparison the general pathological concepts of tissue reaction to injury. From a study of our material and previously published cases we have been impressed by the fact that all lesions were in about the same stages of development and were of relatively uniform character. Even in those cases in which the disease had been present for the longest

* An exception was the case of Allen, in which a large brain hæmorrhage was the cause of death.

period of time, the vascular changes in the brain, as well as other organs, did not appear to be much more advanced than in the cases of shortest duration. However, within rather narrow limits slight individual differences between cases could be detected. As judged by the degree of glial reaction to parenchymal damage and the proliferation of cells in the vessel wall our Cases 1 and 2 presented a somewhat earlier reaction than Cases 3 and 4. In all of these cases the brain lesions seemed to correlate best with symptoms of the terminal phases of the disease, that is, with the acute onset of the hæmorrhagic diathesis or the exacerbation of the illness.

The significance of the fibrotic thickening of the meninges, and the gliosis in the marginal layer of cerebral cortex, in the inferior olivary nuclei, and sometimes in other nuclear structures is doubtful. These changes are not specific and were of such character as to have preceded the acute illness under consideration.

Ætiology and Pathogenesis.—The cause of this disease is as yet unknown. Moschowitz was of the opinion that the thrombi were of the hyaline type and made up of compact masses of erythrocytes. Baehr and his associates formulated the hypothesis that the disease was the result of sensitization of the vascular endothelium with secondary platelet thrombosis, and of thrombopenia due to the withdrawal of platelets from the circulation. They pointed out the resemblance between the vascular lesions in this disease and those which occurred in the veins in the Schwartzman phenomenon. The fact that two of our cases (1 and 4) had had allergic manifestations, as did the case of Engel and others, gives some support to this hypothesis. Appertaining to the matter of sensitivity it is of interest that three of the thirteen reported cases have had urticaria.

The absence of inflammatory exudate, bacteria, or inclusion bodies rules out most infectious agents. The possibility of a bacterial or other toxin acting on the endothelium cannot be as readily dismissed. On the experimental side Kielanowski and Selzer (1937) have demonstrated platelet thrombosis in the vessels of rabbits after the intradermal injection of *B. coli* culture filtrate. This reaction was, however, accompanied by infiltration of neutrophilic leucocytes in the vessel wall, which occurred only in slight degree in our Cases 2, 3, and 4. Also it has been shown by Dameshek and Miller (1946) that the injection of colloidal particles into animals will produce agglutination of platelets and severe thrombopenia.

We agree with Baehr and his associates and with subsequent writers on this subject, that the thrombi are probably composed of platelets. This conclusion is arrived at partly by the exclusion by special stains of other blood elements in the thrombi and not by the positive staining of platelets, which is very difficult in post-mortem material.

The relation of the thrombi to the vascular proliferation could not be settled with finality. In every case there were many cellular vessels which were not thrombosed and also thrombosed vessels without cellular hyperplasia. From available evidence we find it impossible to decide whether thrombosis or endothelial proliferation is the primary event.

Relation of Neurological Symptoms to Brain Lesions.—Our four cases did not have the kind of neurological symptoms that lend themselves to exact clinico-anatomical correlation. The confusion, stupor, coma, and convulsions were indicative of a widespread disorder of the cerebral cortex and basal ganglia and could be related to the widespread vascular damage in these parts of the brain. In those cases showing perivascular necrosis and hæmorrhage in the nuclei of the brain stem there had been no symptoms pointing to damage of these structures. In all probability the lesions were in these cases too small and widely scattered to cause focal neurological symptoms. Perhaps in those cases previously reported in which aphasia, hemiparesis, facial weakness, etc., had occurred there was unusually severe affection of the blood vessels in one region so as to produce a much larger focus of ischæmic necrosis similar to that in the tegmentum of the midbrain in our Case 4. In neither our case nor that of Bernheim in which generalized convulsions occurred was it possible to find the " pseudolaminar degeneration " of cortex which has been observed in some cases of epilepsy.

Differentiation as a Disease Entity.—From the clinical point of view thrombocytic acroangiothrombosis must be distinguished from idiopathic thrombocytopenic purpura, other acute diseases in which there is a hæmorrhagic tendency, and diffuse vascular disease, particularly disseminated lupus erythematosus, subacute bacterial endocarditis, and acute hæmorrhagic encephalitis.

We have studied the pathological material from six cases of idiopathic thrombocytopenic purpura, some of which had been presented by Nickerson and Sunderland (1937) and were unable to find any vascular hyperplasia or thrombosis of the type which occurs in thrombocytic acroangiothrombosis. The marked anæmia so often seen in the platelet thrombosis cases is not usually found in Werlhof's syndrome. Also, there are important clinical differences inasmuch as frequency of symptoms of cerebral

disorder in Werlhof's syndrome is much lower, estimated at about 15 per cent., and when present are almost always related to hæmorrhage into the brain and spinal cord or the meninges (Weisfuse ; see footnote page 40).

The pathological findings in " allergic " purpura and in disseminated vascular disease, that is, post-exanthematous encephalomyelitis, disseminated lupus erythematosus, and periarteritis nodosa, differ from those of the disease under consideration in regard to the brain. In our cases of lupus erythematosus the most striking brain lesions were embolic and were secondary to Libman-Sachs type of verrucous endocarditis. In many respects they resembled the focal necroses in Engels and others' case. Furthermore the subarachnoid arteries were occluded, whereas in thrombocytic acroangiothrombosis the small vessels in the grey matter were exclusively involved. In our cases of lupus erythematosus fibrinoid necrosis of connective tissue and vascular thrombosis or hyperplasia of endothelial cells were not present in the brain. The close relationship of platelet thrombosis and lupus erythematosus and rheumatic fever cannot be denied, but until more is known of the ætiology of these diseases they must be separated.

On morphological grounds alone the occurrence of petechial hæmorrhages in the brain requires that one consider such diseases as pericapillary encephalorrhagia (acute hæmorrhagic encephalitis or hæmorrhagic leucoencephalitis), post-exanthematous encephalomyelitis, fat embolism, and other varieties of brain purpura. So little is known about acute hæmorrhagic encephalitis that it is difficult to construct a clear concept of its clinical and pathological features. Some cases have apparently been the result of the administration of arsenic or some other compound, whereas others have occurred in the course of a virus pneumonia, influenza, or without known antecedents. The outstanding clinical symptoms have been stupor, coma, and convulsions. The cerebrospinal fluid has been normal. At autopsy myriads of petechial hæmorrhages were widely disseminated through the cerebral white matter and to a lesser extent in the white matter of the brain stem. Unlike thrombocytic acroangiothrombosis there have been no hæmorrhages in the skin or other organs, anæmia, or thrombopenia, and the vascular lesions of the brain are dissimilar. Other types of brain purpura and post-exanthematous encephalomyelitis can be readily distinguished by histopathological examination.

It should be pointed out that one of the unique and distinctive pathological features of thrombocytic acroangiothrombosis is the occurrence of prominent vascular lesions with only slight parenchymal lesions. The discrepancy between the marked vascular reaction and the slight parenchymal change was quite remarkable. By comparison the degree of tissue damage was much less than in cerebral fat embolism where vessels of similar size may be occluded. The most likely explanations of this discrepancy are that platelet thrombosis occurred slowly, so that adequate collateral circulation could be established ; and that the occlusion was in many vessels incomplete. Undoubtedly many of the thrombi formed shortly before death so that there was insufficient time for tissue necrosis to become manifest.

Since the real cause and pathogenesis of platelet thrombosis are unknown, one of us (P.F.) has suggested the descriptive term thrombocytic acroangiothrombosis. " This term designates the location of the lesion (acro-terminal, angio-vessel), states the nature of the process (thrombosis-plugging of a blood vessel by clot), and identifies the chief constituents of the thrombus (thrombocytes or platelets) " (Fitzgerald and others, 1947).

Summary

The neurological and neuropathological findings in four cases of thrombocytic acroangiothrombosis are presented. This is a rare disease of unknown ætiology which begins acutely, runs a rapidly progressive course, and usually causes death in a few days or weeks. The leading clinical features were fever, purpura, anæmia, thrombopenia, and symptoms of cerebral disorder such as muscular weakness, hemiplegia, convulsions, confusion, stupor, and coma. The cerebrospinal fluid was normal. The most important pathological changes were a striking increase in cellularity of the walls of arterioles and capillaries and thrombi of platelets. These vascular abnormalities were quite pronounced in the brain of each of the four cases, and were sometimes associated with multiple small foci of parenchymal necrosis and petechial hæmorrhages.

The neurological data of fourteen reported cases are summarized.

Clinically the disease must be distinguished from idiopathic thrombopenic purpura, disseminated lupus erythematosus, subacute bacterial endocarditis, and rickettsial diseases. This usually is possible by taking into consideration the total clinical picture and the laboratory data. The diagnosis of the disease can probably be established by bone-marrow biopsy in which platelet thrombi and vascular hyperplasia can often be seen. The brain lesions are believed to represent a unique picture unlike any other neuropathological type of reaction to disease.

REFERENCES

Allen, A. C. Personal Communication.
Altschule, M. D. (1942). *New Engl. J. Med.*, **227**, 477.
Baehr, G., Klemperer, P., and Schifrin, A. (1936). *Trans. Ass. Amer. Phys.*, **51**, 43.
Bernheim, A. I. (1943). *J. Mt. Sinai Hosp.*, **10**, 287.
Carter, J. R. (1947). *Amer. J. med. Sci.*, **213**, 585.
Dameshek, W., and Miller, E. B. (1946). *Blood*, **1**, 27.
Engel, G. L., Scheinker, I. M., and Humphrey, D. C. (1947). *Ann. intern. Med.*, **26**, 919.
Fitzgerald, P. J., Auerbach, O., and Frame, E. (1947). In the press.
Gitlow, S., and Goldmark, C. (1939). *Ann. intern. Med.*, **13**, 1046.
Holmgren, Hj. (1940). *Z. mikr.-anat. Forsch.*, **47**, 489.
Jorpes, E., Holmgren, Hj., and Wilander, O. (1937). *Ibid.*, **42**, 279.
Kielanowski, T., and Selzer, A., Quot. from G. Schwartzman, (1937). "Phenomenon of Local Tissue Reactivity." Paul B. Hoeber. New York.
Moschowitz, E. (1925). *Arch. intern. Med.*, **36**, 89.
Nickerson, D. A., and Sunderland, D. A. (1937). *Amer. J. Path.*, **13**, 463.
Sylven, D. (1945). *Acta radiol.*, Suppl., **59**, 99.
Trobaugh, F. E., Markowitz, M., Davidson, C. S., and Crowley, W. F. (1946). *Arch. Path.*, **41**, 327.
Weisfuse, L. Personal Communication.

PRIMARY CEREBRAL HYDATID CYSTS

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A review of primary cerebral hydatid disease in Australasia shows that twenty-nine cases of primary hydatid cyst of the brain have been recorded here during the last sixty years. The fact that such cysts are quite rare in countries where hydatid disease is relatively common has been stated previously by Dew (1934). In the opening paragraph of this article, Dew has clearly stated the basis for differentiating this type of cerebral cyst from secondary cerebral infestation : " As in the case of all organs, infestation of the brain with echinococcal disease may be either primary or secondary. In the former, the cysts are derived from hexacanth embryos, which, after passing through the liver and lungs, have been carried by the carotid arterial stream to the brain. Secondary cysts are metastatic, and result from the sowing by the blood stream of scolices, derived from a fertile primary simple cyst which has ruptured into the left side of the heart. It is obvious, although the fact has not been universally recognized, that the pathological and clinical aspects of these two types are very different . . ."

The present article is concerned with an analysis of the twenty-nine recorded Australasian cases, which include five cases from the author's practice. Of the total twenty-nine cases, records of fourteen are contained in the Hydatid Registry of the Royal Australian College of Surgeons, five are recorded here, and the remainder are either referred to by Dew (1928) or have been published in early Australian medical periodicals.

An excellent review of the literature of intracranial hydatids has been published by Langmaid and Rogers (1940), and reference should be made to their article for an historical account of this condition.

Case Reports

Case 1.—A girl aged twelve years was referred to the author on June 25, 1940. This child had lived in the country all her life in a sheep-grazing district. She had been perfectly well until the past year, when she had noticed attacks of giddiness which had become progressively more severe and more frequent and were accompanied by some alteration of visual acuity. In these attacks, objects seemed to rotate in a clockwise direction. In the past six months she began to experience left supra-orbital headache, which was worse on rising in the morning. Two months ago she noticed diplopia on lateral deviation to each side.

The only abnormal sign detected on examination of the nervous system was a complete congruous right homonomous hemianopia with macular sparing. There was no enlargement of the head, and radiographs of the skull were within normal limits. The girl was bright, alert, and intelligent, and co-operated well during examination. There was no papillœdema. The cerebrospinal fluid pressure was 350 mm., chlorides 710 mg. per 100 c.cm. ; there was no increase in globulin, and the protein content was 20 mg. per 100 c.cm. The Casoni reaction and complement fixation test for hydatid were both negative. There was no relative eosinophil leucocytosis. A pre-operative diagnosis of left occipital tumour was made, and a left occipital craniotomy performed. The exposed brain appeared bluish, and an incision into the left occipital region revealed the greyish wash-leather wall of a hydatid cyst. The cortical incision was extended, and the whole cyst removed intact. After removal, examination of the cystic fluid did not reveal any scolices or hooklets. The wound was closed in layers without drainage ; convalescence was uneventful and the patient was discharged from hospital perfectly well three weeks after operation. She has remained quite well, and has been working for some years as a telephonist.

Case 2.—A boy aged ten years was referred by Dr. Holt, Canberra, Australian Capital Territory, on Nov. 9, 1940. He had been perfectly well until nine months previously, when he had a series of generalized convulsions, since when he developed tremor in the left hand, generalized headaches, and occasional early morning vomiting. Apart from these symptoms he appeared quite well. He could swim and ride a bicycle, and was good at his schoolwork. His visual acuity was 6/6 in each eye, there was no papillœdema, but perimetric examination showed a left congruous homonomous hemianopia with macular sparing. There was no other disturbance of the cranial nerves or of the motor or sensory systems.

Plain radiographs of the skull showed some increase in convolutional markings, but were otherwise within normal limits. The cerebrospinal fluid was clear, under a pressure of 300 mm. There was no increase in cells or globulin, the total protein was 10 mg. per 100 c.cm., and the chlorides were 730 mg. per 100 c.cm. The Casoni reaction and complement fixation test for hydatid were negative. A provisional diagnosis of right occipital tumour was made, and a ventriculogram performed by the occipital route. On the right side, at 1 cm. below the dura, yellowish fluid was aspirated. In view of the colour of the fluid, it was considered that the lesion was a cystic glioma, and a bone flap was reflected. An incision was made into the right occipital cortex, and the cyst opened and then found to contain 12 oz. of yellowish fluid and many daughter cysts. Microscopic examination of the fluid showed profuse scolices. Failure to recognize the fact that hydatid fluid might be yellowish had meant that the operation field was now contaminated, and at this stage it was too late to disinfest with formalin solution. The patient made an uneventful recovery, and was discharged from hospital three weeks after operation. He remained well for seven months, and then commenced to suffer from severe generalized headache, following which he became progressively stuporose and died in coma eight months after the operation. Post-mortem examination was carried out twenty-five hours after death. There were no hydatid cysts present in the lungs, heart, or liver. During removal of the brain a large number of hydatid daughter cysts, each about two cm. in diameter, escaped from the right cerebral hemisphere. These cysts were found mainly in the right temporal lobe, but were also present in the adjacent parts of the right parietal and occipital lobes. Death had been due to medullary compression following uncal herniation.

Case 3.—A boy aged eleven years was referred to the Neurosurgical Department of the Royal Prince Alfred Hospital by Dr. Glanville Rawle of Lismore on June 5, 1941. For two years he had shown slowly progressive mental deterioration, and during the past twelve months he had begun to suffer from generalized headaches. In the past two months his visual acuity had gradually diminished.

The child had a large head, a fatuous smile, and monosyllabic, monotonous speech. His mentality was well below the average. The bitemporal diameter of the head was 17 cm., the occipito-frontal diameter 21·5 cm. There appeared to be general widening of the sutures, especially marked over the left fronto-parietal region. Both eyes showed some degree of proptosis, the left being more marked than the right. There was no anosmia, the appearance of the optic discs suggested early papillœdema and the remaining cranial nerves were all intact. There was no disturbance of the motor system, his co-ordination was intact, and all the tendon reflexes were present, slightly increased, and equal on the two sides. The abdominal reflexes were present.

Owing to mental deterioration, he was a poor witness for subjective tests, but no disturbance of the sensory system could be detected, and the visual fields appeared full on confrontation. Radiographs of the skull showed a very large head with widely separated sutures, a "ballooned" sella turcica, and marked thinning of both frontal bones. The cerebrospinal fluid pressure was 300 mm., the fluid clear; there was no increase in globulin, the total protein was less than 20 mg. per 100 c.cm., and the Lange gold curve 0001100000; there was no increase in cells, and the Wassermann reaction was negative. The Casoni reaction and complement fixation test for hydatid were positive, and the eosinophil differential count 5 per cent.

A ventriculogram performed by the occipital route showed considerable shift of a dilated ventricular system to the right side. The left frontal horn did not fill. A diagnosis of left frontal hydatid cyst was made. Craniotomy was performed by the left frontal approach, and the exposed cortex appeared extremely thin and presented a blue-grey appearance. The thin shell of cortex (one or two mm. thick) was removed to uncover the wall of the cyst, and the cyst was needled and a large amount of cloudy fluid gushed out. Eight c.cm. of 10 per cent. formalin was run into the cyst and allowed to remain *in situ* for seven minutes. The contents of the cyst were then completely evacuated, and the cyst was opened and its inner wall painted with metaphen. The wall was then delivered in one piece, and could be stripped away with ease from the adjacent cerebral surface. The volume of the evacuated fluid measured 20 oz.

The patient's condition was excellent throughout the operation, and his convalescence was uneventful. He was allowed out of bed ten days after the operation. Post-operative radiographs showed that the cavity left by removal of the cyst was filled with air, which gradually disappeared over the succeeding week, apparently as the result of expansion of the left cerebral hemisphere.

This patient has been seen from time to time during the past six years, and is at present quite well and has had no recurrence of his previous symptoms.

Case 4.—A boy aged three years and four months had lived in Harden, New South Wales, since birth. He lived on a farm where there were four dogs used in relation to sheep grazing. He was referred to the care of Dr. J. S. Davis at the Royal Alexandra Hospital with a history that he had been limping on the left leg for six to eight weeks and was disinclined to use the left arm. There had been no complaint of headache, no vomiting

and no obvious change in the visual acuity. The child's head was enlarged (circumference 22 inches), and the vault appeared to be more prominent in the right parietal region. Well marked papillœdema was present in each fundus, but there appeared to be no contour defect in the visual fields on confrontation. The left abdominal reflexes and the left knee jerk were absent. Plantar responses were flexor on both sides. The Casoni reaction was negative, and there was no increase in eosinophil leucocytes.

A provisional diagnosis of a right hemisphere lesion was made, and a ventriculogram was performed. Clear fluid was withdrawn from the right side at a depth of 1·5 cm., and it was supposed that a dilated ventricle had been tapped. Air was introduced into the supposed ventricle and the head radiographed. At this stage the author was asked to see the case in consultation, and it was decided that the air had filled a cystic cavity which was probably a cerebral hydatid. A right parietal flap was then reflected, and, after incision of the dura, the typical wash-leather wall of a hydatid cyst was seen presenting on the surface. After the field had been packed off, 5 c.cm. of formalin solution were injected into the cyst, after removal of a similar volume of the cystic fluid. Five minutes later the contents of the cyst were aspirated and the cyst wall delivered intact. The next morning the child had repeated generalized convulsions, and these were controlled with a basal dose of " avertin." Scolices were found in the cyst wall after removal. The child was discharged from hospital five weeks after operation.

Case 5.—A woman aged twenty-three years was referred to the author by Dr. John McGeorge on July 19, 1943, with a provisional diagnosis of cerebral tumour. This patient had never lived in the country, although she had had a good deal to do with dogs, both in her home and elsewhere. She had been perfectly well until twelve months previously, when she began to get occasional generalized headaches. Two to three months before she was seen they had become more severe and were accompanied by early morning vomiting. On three occasions in the early morning she became giddy and had lost consciousness for a period of three to five minutes. There was nothing relevant in the family history, apart from the death of a sister a year previously with tuberculosis. She was married but had no children.

She was a rather masculine type, but was mentally bright and co-operated well during examination. Bilateral papillœdema was present; the left pupil was larger than the right; both reacted well to light and accommodation. There was coarse nystagmus on looking to the left. The remaining cranial nerves were intact, there was some past-pointing to the left with the right hand and some tremor of the left arm. Her tendon reflexes were present and equal on the two sides. The plantar responses were absent on each side. There was no dysdiadokokinesia and no disturbance of gait. Visual field examination showed a left upper congruous quadrantopsia with macular sparing. A plain radiograph of the skull showed considerable enlargement of the pituitary fossa with destruction of the posterior clinoid processes and dorsum sellæ. The cerebrospinal fluid pressure was 420 mm., the globulin was not increased, and total protein was 20 mg. per 100 c.cm. The Casoni reaction and complement fixation test for hydatid were negative.

In view of the visual field defect, it was decided that this patient had a tumour in the right temporal lobe, and a ventriculogram was performed and air introduced into the large cyst in this position. The cyst was very large, extending almost to the cortical surface and medially to the midline. Its anterior-posterior extent was approximately 6 cm. In view of these appearances, it was suspected that it was hydatid in origin, and a right temporo-parietal flap was turned down. The cyst was again tapped, and sterilized by the introduction of 10 c.cm. of 5 per cent. formalin, which was allowed to remain *in situ* for ten minutes. The contents of the cyst were then evacuated. The cyst wall was very thin and friable, and broke up with handling. It could not be removed, and it was then decided to close the wound. The cystic fluid did not show any hooklets or scolices.

Two weeks after the operation the patient developed gross œdema of the face and a bilateral lower motor facial palsy, which subsided rapidly in four days following massive vitamin B_1 injections. She was discharged quite well three weeks after operation. Four months after operation she was re-admitted to hospital and an encephalogram performed, which showed a normal ventricular system. She has been observed at intervals during the past four years, and has had no recurrence of symptoms. She was again admitted to hospital in March, 1947, for a further encephalogram, and again the ventricular system was seen to be normal.

General Considerations

The main features of the preceding five cases reported from the author's practice are abstracted and are included in the Table with the previous twenty-four cases in the Australasian literature. Primary cerebral hydatid cysts are single and are due to the passage of a hexacanth embryo through the hepatic and pulmonary circulation with ultimate embedding in a cortical capillary. According to Dew they are at least seven times more common in children than in adults, for he says that cerebral hydatid cysts form 4·9 per cent. of all organ infestations in children, and 0·7 per cent. of all organ infestations in adults. The relative frequency in children in this series appears very much higher, since only two cases out of twenty-nine were above seventeen years of age. The hemisphere involved would appear to be quite fortuitous. Dew has suggested, though he qualifies his statement by saying that there are not sufficient statistics for adequate deductions, that the left carotid would receive the larger percentage, and that primary cysts should be more frequent in the left cerebral hemisphere. In this series, of the twenty-eight cysts in the cerebral hemispheres, fifteen were found

on the left side and thirteen on the right. The one cerebellar cyst reported was on the left side. It would seem that from these figures no deduction may be drawn, except that relative infestation of the two sides is about equal. It is remarkable that the nine New Zealand cases all occurred in the right hemisphere, and sixteen of the twenty Australian cases occurred on the left side.

Dew (1928) has already pointed out that the parietal lobe is the most frequent site for primary cerebral hydatid cyst; the present series shows the following distribution:

Frontal	2
Parietal	14
Parieto-occipital	5
Temporal	2
Occipital	5
Cerebellar	1
	29

It should be remembered, however, that these cysts are often so large that they overlap the boundaries of cerebral lobes, and may not infrequently occupy the parieto-temporo-occipital region of one half of the cranial cavity. It is more useful, therefore, to compare a pre-rolandic with a post-rolandic distribution. By far the greater number of cysts are found in the vascular field of the middle cerebral artery, and consequently come to lie mainly behind the fissure of Rolando. This might be expected from the relative size of the middle cerebral artery compared with the smaller lumen of the anterior cerebral and posterior communicating vessels, and from the nature of the origin of the middle cerebral artery from the internal carotid.

In this series the hemisphere cysts were distributed as follows:

Pre-rolandic	2
Post-rolandic	26

As the cyst grows, it displaces the cerebral substance and adhesions do not tend to form between the brain surface and the adventitia of the cyst. For this reason, the whole cyst wall may usually be delivered with care, after sterilization and partial evacuation, by gentle traction with wide-tipped forceps, such as the sponge-carrying type. The rate of growth of hydatid cysts of the brain is probably quicker in the brain than in other organs, at least in the early stages before an increase in intracranial pressure has taken place. In Case 3 reported above, multiple cysts were found at autopsy to have reached a maximum diameter of 2·5 cm. eight months after an operation for removal of the primary cyst during which the operation field was sown with scolices. It may be concluded, therefore, that a primary cerebral hydatid cyst of 2·5 cm. diameter had been sown in the brain approximately six to twelve months previously.

The cyst is usually perfectly circular in shape, and, if it does not actually present on the surface, it will be found to be covered by not more than a few millimetres of compressed cortex. In some cases actual erosion of the overlying cranial vault may be found, and this fact should be remembered in studying skull radiographs. In one case the cyst had eroded through the calvarium and was presenting beneath the scalp. The wall of the cyst has a characteristic anæmic wash-leather appearance, and is usually about 2 to 3 mm. thick. Its laminated character is certain evidence of hydatid pathology. The cyst contents may or may not include scolices, hooklets, or daughter cysts. The cyst is often sterile, and daughter-cyst formation is infrequent. The hydatid fluid in these cysts is usually perfectly clear, and may at operation be indistinguishable from ventricular fluid. Occasionally it may be cloudy or even yellowish in colour. The saline content may or may not be increased.

Diagnosis

Even in a country where hydatid disease is relatively common, the pre-operative diagnosis of a primary cerebral hydatid is uncommon. This might be expected in the first instance from the relative infrequency of primary cerebral infestation, and precise diagnosis is made difficult by the fact that many patients do not exhibit any specific local or general evidence of hydatid infestation. In only one case (25) in this series were the specific hydatid reactions positive, and it is not surprising that in the twenty-nine cases a pre-operative diagnosis of primary cerebral hydatid cyst was made in only eight cases.

The symptomatology usually implies the presence only of some space-occupying lesion causing increased intracranial pressure, and, even after exhaustive investigation which may confirm the presence and position of the lesion, its nature may not be proved until a craniotomy has been performed and the wall of the cyst exposed. However, the general clinical picture is sufficiently uniform for suspicion of a hydatid lesion to be aroused whenever such a picture is seen in a child referred from a sheep-grazing district. If one is not aware of this possibility beforehand, the intracranial field may be sprayed with scolices through the performance of a ventriculogram or an improperly planned operation (Case 2).

The average age at which symptoms present themselves is important in diagnosis. In this series,

TABLE

Case No.	Aust. Reg.	Patient	Sex	Age (years)	Surgeon	Place	Signs	Duration	Situation	Size	C.S.F. pressure	Specific reaction	Pre-operative diagnosis	Date	Result
1	—	C.G.	M	16	C. P. B. Clubbe	R.P.A.H., Sydney	Headache Vomiting Papillœdema	Several weeks	L. parietal	4" dia.		—	Cerebral tumour	March, 1890	Recovery
2	—	—	M	9	L. D. Parry	Young, N.S.W.	Blindness Giddiness Headaches Hemiplegia	8 months	L. parietal	—		—	Cerebral hydatid	17th June, 1892	Death
3	—	C.S.G.	M	12	W. Chisholm	R.A.H.C., Sydney	Headache Vomiting Dimness of vision Hemiparesis	6 years	L. parietal	19½ oz.		—	Cerebral hydatid	17th Sept., 1893	Death
4	—	E.J.	M	11½	G. A. Fisher	Adelaide Hospital	Headaches Vomiting Papillœdema	Several years	L. parietal	—		—	—	No operation Autopsy	Death
5	—	E.W.	F	9	L. Fitzpatrick	Dubbo	Visual deterioration Headaches	2 years	R. parieto-occipital	10 oz.		—	Cerebral hydatid	1894	Death
6	—	T.H.G.	M	13	W. H. Crago	Sydney Hospital	Headaches Vomiting Mental deterioration Papillœdema	6 years	L. frontal	—		—	Left frontal tumour	13th Feb., 1900	Recovery
7	—	A.R.	F	17	B. Poulton	Adelaide Hospital	Vomiting Headaches Hemiplegia Papillœdema	—	L. parietal	4" dia.		—	Hydatid cyst	12th Jan., 1903	Recovery
8	—	R.C.	F	6	A. McCormack	R.P.A.H., Sydney	Headaches Hemiparesis Papillœdema	4 years	L. parietal	Goose's egg		—	Cerebral hydatid	18th April, 1904	Recovery
9	659	I.H.	M	10	Grieves and Downes	Ch. Hosp. Melbourne	Convulsions Headache Hemianopia	—	L. temporal	Large lemon	260	—	—	17th Dec., 1935	Good
10	1551	M.N.	M	3	F. Morgan	St. Vincents Hospital, Melbourne	Vomiting Ataxia Papillœdema	6 months	L. parieto-occipital	Large orange	—	—	Cerebellar tumour	4th April, 1941	Death
11	257	D.F.	M	15	Nelson and Dew	R.A.H.C., Sydney	Failing vision Vomiting	5 months	L. parieto-occipital	—	—	—	—	15th Mar., 1927	Still alive
12	259	M.X.	F	44	Hailes	Melbourne	Headache Vomiting Hemiparesis	6 months	L. temporal	—	—	—	—	7th Sept., 1933	Success
13	—	M.H.	M	4	Britten Jones	Adelaide Hospital	Vomiting Meningismus	5 weeks	L. cerebellar	—	—	—	—	—	Death
14	1580	R.B.	M	8	—	N.Z.	Paresis Ataxia Papillœdema	5 months	R. parietal	—	—	—	—	31st May, 1940	Death after two years
15	1197	L.D.	M	9	Robertson and Christy	N.Z.	Not recognized	3 years	R. hemisphere	Large orange	—	—	Unsuspected	22nd Oct., 1937	Death in 36 hours

TABLE (*continued*)

Case No.	Aust. Reg.	Patient	Sex	Age (years)	Surgeon	Place	Signs	Duration	Situation	Size	C.S.F. Pressure	Specific reaction	Pre-operative diagnosis	Date	Result
16	1232	S.L.	M	5	Williams	N.Z.	Headache Vomiting Convulsions(2) Cerebellar syndrome	Few months	R. occipital	—	—	—	Hydrocephalus	—	Death
17	1385	V.M.	F	5	Williams and Bell	N.Z.	Cerebral symptoms	3 years	R. hemisphere	Large	—	—	Suspected hydatid	12th July, 1938	Death
18	983	M.M.	F	6	Burns	N.Z.	—	—	R. motor cortex	Small	—	—	—	5th Sept., 1916	Well after twenty years
19	130	J.L.S.	M	8	Barnett	Dunedin, N.Z.	Visual deterioration Paresis	—	R. rolandic	—	—	—	—	17th Aug., 1914	Alive after twenty years
20	410	M.S.	F	14	Burns	N.Z.	—	—	R. occipital	—	—	—	—	—	Death
21	1214	T.G.	M	—	Barnett	Dunedin, N.Z.	—	—	R. rolandic	Small orange	—	—	—	17th Mar., 1896	Well for some years
22	—	R.B.	M	8	Hutchison	Wanganui, N.Z.	Papillœdema L. hemiparesis Mental dullness	5 months	R. parietal	—	—	—	R. parietal tumour	31st May, 1940	Died with second cyst 13th Mar., 1942
23	1819	D.M.	F	4	Nelson, T. Y.	Sydney	Headaches Vomiting Papillœdema	9 months	L. parieto-occipital	200 c.cm.	—	Not done	Craniopharyngioma	6th April, 1945	Died 10th April, 1945
24	1549	H.M.	F	13	Coates and Hollycock	Melbourne	Headaches Vomiting Papillœdema Fits (2)	2 years	L. parieto-occipital	1 large 4 small	—	—	Cerebral tumour	28th Nov., 1940	Well 12 months later
25	—	K.H.	M	11	Phillips and Reid	R.P.A.H., Sydney	Visual deterioration Headaches Physical and mental deterioration	2 years	L. frontal	20 oz.	300	Casoni+ Complement fixation+	L. frontal hydatid cyst	2nd Nov., 1941	Alive and well after six years
26	—	B.H.	F	12	Phillips	R.P.A.H., Sydney	Hemianopia Diplopia Giddiness Headaches	1 year	L. occipital	15 oz.	350	—	Occipital tumour	26th May, 1940	Alive and well after seven years
27	—	I.T.	M	10	Phillips	R.P.A.H., Sydney	Convulsions Headaches Vomiting Tremor Hemianopia	9 months	R. occipital	12 oz.	300	—	Occipital tumour	5th Oct., 1940	Death after eight months
28	—	C.G.	M	3½	Shedden-Davis and Phillips	R.A.H.C., Sydney	Paresis Vomiting Papillœdema	2 months	R. parietal	10 oz.	—	—	Cerebral hydatid	15th Mar., 1944	Alive and well
29	—	D.B.	F	23	Phillips	R.P.A.H., Sydney	Headache Vomiting Papillœdema Hemianopia	1 year	R. parietal	15 oz.	420	Post-op. anaphylactic œdema	R. occipital tumour	5th Aug., 1943	Alive and well after five years

the extremes range from three to forty-four years. However, eighteen cases occurred in the decade from seven to seventeen. The average age at operation lies between nine and ten years, premonitory symptoms usually arising one or two years previously. Even in Case 10 (aged three) the symptoms had been present for six months, and, as the cyst was described as being the size of a large orange, it had probably been sown in this patient's brain at about the age of eighteen months. There is a preponderant infestation of males as against females in a ratio of eighteen cases to eleven cases in this series.

The cardinal symptoms in practically all the cases are those due to increased intracranial pressure, particularly vomiting and headache : one, or more commonly both, of these symptoms were present in every one of the cases. Their character is identical with the same symptoms produced by intracranial neoplasm. The headache is usually generalized and appears on rising in the morning. Vomiting, which also tends to occur in the early morning, is projectile, is not preceded by nausea, and may relieve the headache. There may be, and usually are, no other symptoms, at least in the early stages. Visual deterioration, which is either due to optic atrophy following papillœdema or to hemianopia, is a fairly constant late symptom. Unilateral weakness is common as a late symptom, and may be associated with a history of convulsions. Less commonly, as a late manifestation, cerebellar symptoms may be present, as they were in two of the author's cases, and may constitute a false localizing sign suggesting the presence of a lesion in the posterior fossa (see also Case 10).

The signs of primary cerebral hydatid cyst relate chiefly to the increase in intracranial pressure, and it is rare that the patient is proved in the first place to be the host of a hydatid cyst in another situation. Autopsy in Case 27 did not reveal evidence of hydatid infestation anywhere else in the body, and a number of previous autopsy reports in patients who have died from primary hydatid cyst of the brain have rarely shown the presence of hepatic or pulmonary lesions. Those who live after operation have usually done so for many years, a fact which indicates that the cerebral cyst was single, both in the brain and the body. In most cases where the Casoni and hydatid precipitin reactions were examined they were found to be negative. In Case 25 they were both positive. The non-specific signs include papillœdema, a large head, not infrequently a cracked-pot sound on percussion, and radiographs which show convolutional thinning, separation of sutures, or erosion of the sella turcica. Local thinning of the calvarial vault may occasionally be seen. Calcification of the pineal gland is unusual in children, so that lateral shift may not be detected radiographically. Calcification has not been recorded in a primary cerebral hydatid cyst. Hemianopia may be a useful sign, and was found in three of the author's cases before operation. From the situation of the cyst in Case 28 it may be deduced that hemianopia was probably present there as well, but the patient was too young for accurate subjective examination. Signs of pyramidal disturbance may be seen in convulsions or paresis ; tremor, ataxia and nystagmus occurred in a number of cases due to involvement of the extrapyramidal circuit from cortex to cerebellum.

Individual symptoms and signs may now be examined in some detail.

Headache, Vomiting, and Papillœdema.—This group of pressure symptoms may conveniently be taken together. As one might expect in a group of people whose average age is at the beginning of the second decade in life, vomiting was the commonest sign in the pressure group. Characteristically projectile, it was typical in other respects in its appearance early after rising in the morning, and in the relief of the morning headache which succeeded vomiting. Headache was nearly as common, was generalized, and had the characteristic early morning incidence of a pressure headache. Papillœdema was less common, being recorded in eleven of the twenty-nine cases, the low incidence no doubt being due to the separation of sutures which may occur in this age group. The pressure group of symptoms is, however, most important, as one or more of the three may be the only evidence of a primary cerebral hydatid cyst in a child, and even exhaustive investigation may not reveal any other significant sign.

Visual Disturbances.—In the records of the early cases, visual disturbance is usually stated simply as visual deterioration, and in only one case (Case 9) had hemianopia been reported, though it was observed in three of the author's five cases. There is little doubt that in these children, particularly in the late stages, visual deterioration will occur as the result of secondary optic atrophy following papillœdema. However, as stated previously, with a focal distribution of thirteen to one in favour of a post-rolandic site, and with lesions which usually contain from ten to twenty ounces of fluid, an early high incidence of hemianopia is to be expected. As the defect will be due to interference with the supra-geniculate pathway, macular sparing should

be typical and central vision therefore is unlikely to be affected. However, the child may be aware of some change in visual capacity, which he is probably unable to assess or describe, and which may therefore be exhibited wholly by errors in school work and a tendency to bump into objects on the side of the visual field defect. There is probably little doubt that in the majority of primary hydatid cysts in the cerebral hemispheres a careful perimetric examination will disclose a congruous hemianopia with macular sparing, and if this is found in association with signs of increased pressure a diagnosis of primary cerebral hydatid cyst becomes more likely. At this age, and in this situation, other lesions become even less common than primary cerebral hydatid cyst.

Pyramidal Disturbances.—Motor disorders may take the form of paresis, tremor, or convulsions. Paresis is by far the most common, having occurred in twelve cases in this group, in most instances involving the contralateral arm and leg equally. In a few cases tremor of the paretic limb was the first sign of pyramidal defect. It is unusual that in this age group convulsions were not more commonly seen, having been reported in only one of the author's cases and in three cases previously. Unfortunately, electroencephalographic studies are not available in any of this material.

Mental Deterioration.—In seven cases, some form of mental deterioration has been observed, and it is notable that this was present both in the frontal cysts and in the post-rolandic cases ; it was usually seen in a patient in whom symptoms had been present for a long time or in whom the cyst was a large one.

Cerebellar Signs.—These include ataxia, nystagmus, and intention tremor, and they may be false localizing signs. Mild defects suggestive of cerebellar dysfunction have been recorded in a number of cases, and it has been suggested that they may be due to pressure on the ipsilateral cerebellar hemisphere from the large cystic collection lying above the tentorium. That this is not the explanation may be deduced from the fact that the apparent cerebellar disturbance is on the opposite side to the cyst in the cerebral hemisphere, and it is probably interference with the temporo- and occipito-pontine fibres relaying into the neocerebellum that produces disturbance of co-ordination and decomposition of movement, particularly in the upper extremity on the opposite side of the body.

Surgical Treatment

The surgical removal of primary hydatid cyst of the brain is a simple procedure and offers few technical difficulties. The skull is usually thin, and a large bone flap may be reflected in most cases without any blood loss, as the bone itself and the intracranial field are both relatively avascular. In one of my cases the bone was so thin that the flap could be cut down with strong scissors. The dura having been reflected, the wall of the cyst may be found to present on the surface, or may be covered with avascular cortex which is not more than a few millimetres thick and which may therefore be split in a linear fashion to expose the firm anæmic wash-leather membrane whose appearance is sufficiently characteristic to establish the diagnosis in most cases. When the cyst is recognized, the exposed cortex should be covered by overlapping wet lintine strips covering the whole area with the exception of a small point on the cyst wall.

Five c.cm. of 10 per cent. formalin are now placed in a 10 c.cm. syringe. A fine needle is attached to the syringe, and, after insertion through the cyst wall, 5 c.cm. of cyst fluid is withdrawn slowly into the syringe. The contents of the syringe are now injected, without pressure, into the cavity of the cyst. It is wise to have a loose piston in the syringe, and to allow the formalin-cyst fluid mixture to run back by gravity. Two or three c.cm. may remain in the barrel. The needle may then be withdrawn and a lintine patty placed over the point of its insertion. The formalin should be allowed to act in the cyst for ten minutes before any other step is taken.

To remove the formalin, a rubber-type syphon may be attached to a needle reinserted into the cyst wall and the contents syphoned off into an open vessel held away from the operation field. During this procedure the cyst wall tends to collapse away from the surrounding brain tissue and cerebral pulsations of large amplitude begin. Through a second needle inserted into the cyst, further irrigation of the cyst contents may be carried out through the syphon. It is difficult to remove all the fluid within the cyst, and an opening should be made into the wall at this stage at the highest point presenting. The remaining fluid may then be aspirated with a sucker under direct vision. The interior of the wall may then be painted lightly with formalin or metaphen, if the aspirated fluid shows the presence of hooklets or scolices.

The cyst wall may now be withdrawn by gentle traction, care being taken to see that no large veins have become trapped in the collapsed folds of the

cyst. In nearly every case, gentle steady traction of the wall by a pair of sponge-holding forceps in each hand will deliver the cyst in one piece without any damage to the surrounding brain tissue. At this stage the cavity may be lightly filled with saline and the field closed in the usual manner.

The anæsthetic of choice is rectal avertin, which not only reduces the intracranial pressure during operation, but keeps the patient at rest for some hours after, during the early expansion of brain tissue to fill the cavity, which may have contained as much as a pint of fluid. This expansion is usually complete, and post-operative encephalograms have revealed a normal ventricular system in several cases.

The chief difficulty lies in the approach to operation. If hydatid cyst is expected, air studies should not be carried out. Localization may usually be made from the clinical picture, and a bone flap should then be reflected and the cyst wall inspected. The fundamental principle involved is to avoid contamination of the field by scolices, either at operation or by such procedures as ventriculography, or by an attempt to aspirate the cyst through a single burr hole.

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References

Dew, H. R. (1934). *Surg. Gynec. Obstet.*, **59**, 321.
——(1928). "Hydatid Disease." Australasian Medical Publishing Co. Sydney. p. 353.
Langmaid, C., and Rogers, L. (1940). Intracranial Hydatids : *Brain*, **63**, 184.

THE CLINICAL CHARACTERISTICS, TREATMENT, AND REHABILITATION OF REPATRIATED PRISONERS OF WAR WITH NEUROSIS

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Introduction

At the end of May, 1945, we were seconded from Mill Hill Emergency Hospital to start a neurosis centre for repatriated prisoners of war at Dartford, Kent. During the following eight months 811 repatriates from the North-west Europe sector passed through the unit. This paper describes the clinical characteristics of these men, their treatment and rehabilitation, and the results of a short-term follow-up on a sample of them.

The patients were referred to us by the psychiatrists of the 45th Division, who handled the psychiatric problems of the 100,000 British repatriates from Europe. They were men who had shown signs of psychological maladjustment on repatriation, during the repatriation leave, or on returning to their unit after the leave. Mild cases were dealt with on the spot, so that the material sent to us constituted the most maladjusted 1 per cent. of the entire prisoner-of-war group. There were no officers sent to our unit.

The subject is discussed under four headings : clinical characteristics, treatment, follow-up, and general discussion.

Clinical Characteristics

We were already familiar with the main problems facing this group, having seen some twenty patients who had escaped or been repatriated on medical grounds. Based on this experience, a standard case form was drawn up, which we hoped would supply us with the usual psychiatric case data, and also allow us to analyse the results by statistical methods. In order to obtain as much objective information about these patients as possible, we studied in a sample group the physiological response to a standard exercise on a bicycle ergometer, their persistence as measured by leg-raising and breath-holding tests, their suggestibility by the body sway test, and their physique. The details of symptomatology and the exercise response, and the interrelations between these two and physique are discussed in the paper at p. 61 of this issue (Tanner and Jones, 1948) ; only the main results necessary for the understanding of the clinical problem are given here.

The symptoms and history of a sample of 100 of these 811 men were studied. Fifty were seen by each psychiatrist, and the 100 were chosen simply as every fifth admission to the unit. They were examined during the period June to September, 1945. The mean age of the 100 was 27·3, with a standard deviation of 4·0 years. Excluding eight old soldiers, the average time of army service was five and a half years, with a standard deviation of one year. An average of four years had been spent overseas, and three and a half years as prisoner of war. No significant differences exist between the two groups of 50 in age, time of service, or of imprisonment, physique, oxygen consumption following standard exercise, and other physiological tests. Despite an alternating method of selection, however, the groups differed in intelligence (progressive matrices test, $P < \cdot 01$).

Case Form.—The form used followed the familiar pattern of a case history, divided into the three main sections, pre-army, army service, and present illness. At the end of each of these sections certain summarizing items were rated, using a seven-point interval scale, in which a score of one represented the minimal, and seven the maximal degree of severity.

1. Pre-army Record.—Under this heading were considered family history, personal history (home atmosphere, social circumstances, schooling, work record, sexual and marital history), and personality (social adjustment, adaptability, range of interests, temperament, intelligence, physique, etc.). At the end of this enquiry (or later in summarizing the entire history) ratings were made of environmental stress, constitutional predisposition to breakdown, heredity, total stress to

time of joining army, and stress reaction up till this time, that is, the amount of neurotic symptomatology which had occurred. Table I shows the mean ratings of each investigator in these traits, the rating 1 symbolizing little stress, little predisposition, etc.

TABLE I

PRE-ARMY RATINGS

	M.J.	J.T.
Environmental stress	1·9	3·7
Constitutional predisposition ..	2·1	3·2
Heredity	1·9	2·4
Total stress	1·7	3·5
Stress reaction	1·5	2·2

It is unfortunate that we have to present this table first: these ratings, in fact, are the only ones, out of a total of 86, for which the investigators do not agree, and that quite closely. The agreement and reliability of the ratings are discussed in the second paper. After initially discussing the case form, and our definitions, we did not at any time, formally or informally, discuss ratings or our results, and in this particular instance it led to misunderstanding. M. J. rated pre-army traits in relation to what was expected of a neurotic population (whose mean would thus be about 3·5), while J. T. rated them in relation to a normal group. When this is borne in mind the conclusions appear consistent and obvious, and they were supported by the unanimous opinion of the rest of the unit's staff: these patients had not the constitutional predisposition of the usual neurotic seen in neurosis centres, and were only very slightly, if at all, more predisposed than the normal citizen. They had been subjected to no abnormal stresses in civil life, and in conformity with this, had shown no degree of neurotic response.

2. Army Service.—Following a history of army and P.O.W. life, ratings of the following were made: pre-capture army adjustment, unsuitable work in army, home worries, active service physical danger, physical health, prisoner-of-war camp stress, repatriation stress (home and army). The prisoner-of-war camp stress was rated according to the patient's own account of his prison life, but with reference to the objective stress as presumed by the investigator, rather than the repatriate's subjective rating of it. Thus a man who stayed permanently in one camp and was only very slightly starved and never suffered or witnessed any brutaliites was rated 1, while a man who had been shifted from place to place, starved, marched across Germany and beaten up got a higher rating. Table II shows these items.

Though it would not necessarily follow from the manner of making the ratings, we feel that the order of importance of the various items is as appears in the Table. The agreement between raters is satisfactory here. Most important in causing breakdown were the stresses of the camp (and in particular the last six months, with the dislocation of food service, the forced marches,

TABLE II

ARMY SERVICE

	M. J.	J. T.
Prisoner-of-war camp stress ..	3·6	3·5
Repatriation stress (army) ..	3·5	3·7
Repatriation stress (home) ..	3·3	3·9
Active service danger	2·9	3·0
Physical health	2·3	2·5
Army adjustment	2·0	2·5
Home worries	1·8	2·0
Unsuitable work	1·3	1·9

and the bombing), and the difficulties in adjustment both to home and army conditions. The army adjustment of these men, as might be anticipated, was relatively good, and 65 per cent. stated they could think of no better employment in the army than that which had been chosen for them.

The men were also asked to state the three most severe stresses they had been subjected to while in the army. As one of the three 58 per cent. mentioned poor food at the beginning and end of captivity, 30 per cent. stress of active service, 26 per cent. allied bombing as prisoners of war, and 24 per cent. the conditions on the marches at beginning and end of captivity. In response to the specific questions in the case form, 88 per cent. stated that sex *per se* (that is, the lack of intercourse) was no real problem for them while prisoners. This reaction is in marked contrast to that following deprivation of food, when dreams of eating food and group discussions at which such men as butchers and bakers described at length and in detail their dealings with food were common. Eighty-two per cent. said enemy propaganda had no effect on them at all (partly because of the nearly universal access to an illicit radio and British news) and 58 per cent. said they had been subjected to no unreasonable degree of punishment or cruelty.

3. Symptomatology.—The account of the present illness was extended by enquiry about the presence and severity of a total of 64 symptoms, set out in detail in the subsequent paper. There was very good agreement between the investigators on the ratings, and in particular those for the more marked symptoms. Only two symptoms were given a mean rating of over 3·0 by each investigator: these were lack of concentration and depression. The following were given ratings of over 2·5 by one and over 3·0 by the other: feeling of not belonging since repatriation, asocial, more shy in the presence of women than previously, more easily fatigued, breathlessness on effort, effort intolerance, trembling, and resentment towards army and authority in general. These constitute the main symptoms of our group.

Some of the symptoms which rated very low are also of interest. The following were given mean ratings of under 2·0 by both investigators: fear of impotence, actual impotence, fear of sterility, family felt to be less affectionate, battle dreams, weeping, enuresis, frequency of micturition, left chest pain, fainting attacks, flatulence, diarrhœa, and vomiting.

4. Clinical Score.—Finally, instead of making a clinical diagnosis, which has distinct limitations from the descriptive point of view, we rated the patient in the common designations of somatic anxiety (anxiety with somatic symptoms predominating), psychic anxiety (mental distress manifest in lack of concentration, etc.), and depression. We had no patients where the major clinical label was hysteria or psychosis. The mean ratings are shown in Table III.

TABLE III

CLINICAL SCORE

	M. J.	J. T.
Somatic anxiety	2·8	3·1
Psychic anxiety	3·3	3·4
Depression	2·6	2·6

Physiological and Psychological Tests.—It suffices to say here that the exercise response of these patients fell mid-way between that of normal army men and the usual army neurosis centre patient. The same is true of psychometric test results (Eysenck, 1947, p. 255).

Relations between Ratings.—The correlations were calculated between the ratings on the clinical scores and various other ratings and measurements. Few of these reached significant levels, and only two relations are consistent for both investigators, and of interest. *Depression* correlated +0·39 with prisoner-of-war camp stress, and somatic *anxiety* correlated +0·38 with constitutional predisposition. It would seem from our evidence, such as it is, that reactive depression is well named. However, in view of the negative findings in the second paper, we would not lay much emphasis on this.

Treatment

General.—The unit consisted, for most of its existence, of six separate blocks of fifty beds, each with its own doctor and about six nurses. There was in addition a vocational psychologist, a full-time disablement-rehabilitation officer (D.R.O.) of the Ministry of Labour, a psychiatric social worker, and an occupational therapist. Individual psychotherapy followed the usual lines, and physical adjuncts in treatment such as electric convulsion therapy and sodium amytal were used when indicated, which was seldom. The average time the patient stayed was six weeks, and there was only a small variation round this figure.

Each block rapidly became a small community, with its four wards as the basis for smaller groups. It was immediately and strikingly obvious that the morale of this community was of the utmost importance for the outcome of the patient's stay. Patients, particularly the older and more intelligent ones who served to induct newcomers into this new but transitional society, and also nurses contributed to the building of high morale. It was, however, chastening to observe that the chief factor was the behaviour of the psychiatrist. A falling-off of group morale was perfectly perceptible when the psychiatrist began to slacken the pace of his work, or became even mildly preoccupied with outside affairs. It appeared of more importance for him to give the appearance of caring about the welfare of his patients than actually to see them individually at frequent intervals. During the first two weeks of the unit's existence there were only two psychiatrists and a hundred patients arrived ; consequently patients waited up to ten days for their first full interview, but the doctors were on the wards for longer hours than at any subsequent time, and morale was at least as high.

Group Talks.—Each block met from 9 to 10 a.m. every day for a group discussion. These discussions were largely educational in their aims : their use has been described more fully elsewhere (Jones, 1944). Two days were devoted to talks on the structure and function of the central nervous system, and the mechanism of the production of such symptoms of anxiety as headache, fainting, left chest pain, palpitation, and indigestion. On a third morning a documentary film was shown, followed by a discussion : the films served two purposes, reorientation to present circumstances in this country (child welfare film, building trade film) and psychotherapeusis (rehabilitation of physically injured at Roehampton). The fourth morning was devoted to psychodrama, and group discussion, and the fifth to a " grouse meeting," at which the affairs of the community were discussed. This last meeting was found to be of great importance, and provided considerable opportunities for the release of aggression ; it was noticeable that by far the largest number of complaints related to food, about which, from time to time, a somewhat paranoid attitude developed, as noted by Whiles (1945).

Work Therapy and Vocational Selection.—From 10 a.m. to mid-day and from 2 to 4 p.m. the patients were taken by bus to various occupations outside the hospital. Within a few months of our arrival we had found over fifty firms and employers willing to help us in employing the patients in a real work environment (Jones, 1946). The men were not expected to do productive work and did not replace a workman ; but they were afforded an opportunity of seeing the conditions of work in a particular trade, and were expected to lend a hand when required. The effect of this therapy was twofold. The repatriates were able, from a secure and partially secluded base, to re-enter for short testing periods

the society they were endeavouring to return to, and to re-enter it under the natural conditions of association on a job, this helping them to overcome their withdrawn " don't belong " attitude. Secondly, the first-hand contact with a particular job was invaluable in those cases—and they were a majority —where the future employment goal was still uncertain. The range of choice of occupation included farming, dairy farming, market gardening, building, garage work, engineering firm work, foundry work, agricultural engineering, shipyard work, paper mills, chemical factory, printing, clerical, and numerous small shopkeeping jobs. The big factories offered many specialized jobs such as electrical maintenance, heating, print-room, and so forth, so that the total choice of occupation represented a fair cross-section of any small community. A change of job was made when a man requested it, provided the doctor and the psychologist thought it really desirable, and this practical aid to vocational selection was considered by the psychologist to be more valuable than the routine vocational aptitude tests.

Social Rehabilitation.—The repatriates were usually uneasy in crowds, and particularly shy with women. The nurses were of paramount importance in helping to overcome the men's lack of social confidence. Several writers (Newman, 1944; Torrie, 1945), one himself a prisoner of war, have emphasized the repatriate's fear of rejection by women and his feeling of inadequacy in their presence; symptoms which, if not dealt with properly, tend to generate a protective jealous, wronged, mildly paranoid outlook. The nurses, under the psychiatrists' supervision, were actively engaged in therapy at this level. They were often able, with their special training, temporarily to take the place of the repatriate's family and thus allow him to work through his initial diffidence without meeting the defensive reaction that many an uninformed and emotionally concerned wife or fiancée would have shown. We believe that far too little use of nurses has been made in psychiatry in the past; if properly trained and working in close collaboration with the doctors, they can do invaluable work at this social level. We have always held that nurses should be assigned a definite number of patients each, and should read the doctor's notes on these men, and that the doctor should have a tutorial at least once a week to supervise and give advice to the nurses on their handling of them. No attempt is made to hide these facts from the patients and it is not our experience that they resent it in the least; on the contrary they appear to feel gratified that the nurse understands their difficulties better for her instruction. Needless to say, however, such a policy needs good nurses to carry it out, and some are found to be temperamentally unsuited to it.

The nurses ran a dancing class exclusively for non-dancers, and this was found to be very popular and very excellent in its results. From it the men graduated to full participation in a fortnightly social evening. Each block invited girls from one of the local factories once a fortnight; the patients themselves made all the arrangements for these dances, and spent long hours decorating their block and buying prizes, and organizing transport and food for their guests. These socials were as a rule very successful; the welfare officer at the factory concerned organized the party of girls sent, and explained the need to help the shy and inhibited and depressed men, as well as the more sociable patients.

Finally, social relations were frequently discussed in the groups and enacted in the plays, and further insight was fostered in this way.

Placement.—The work therapy helped greatly in determining the placement of patients when they left hospital after discharge from the army. We were fortunate in having a full time disablement rehabilitation officer of the Ministry of Labour, who saw patients likely to be recommended for discharge from the army during the first two weeks in hospital, and on at least one subsequent occasion before they left. He was helped not only by the psychiatrist and vocational psychologist, but had the advantage of a report from the employer with whom the patient had been working while still in hospital. For instance a man who had already seen something of the work of bricklayers, plasterers, etc., on a building site as part of his work therapy, and had done satisfactory work, could be recommended for a Government training with more confidence than a man who wanted a training, say as a plasterer, but had no clear idea of what the work entailed. Our aim was to arrange a definite employment before discharging a patient from hospital, but as the follow-up study shows, we fell far short of this ideal.

Follow-up Study

A follow-up study was carried out on 100 of our patients. Unfortunately it was impossible, for administrative reasons, to obtain a random sample; of the 107 patients who had a London residence the first 100 to be studied constituted our material. They were visited by a psychiatric social worker from three to five months after discharge; in 41 cases both patient and relatives were seen, in 10 cases patients only, and in 49 relatives only. The visits were unannounced, which accounts for the number of men away when visited. The psychiatric social

worker used a standard form drawn up by the psychiatrist as the basis for her enquiries.

In a few cases the relatives were considered to be unreliable informants, though the majority were very helpful. Most appeared to understand the purpose of the visit, and were able to give a good account of the patient's condition. Where the relatives' account seemed to be highly subjective or if they described the patient as no better, or worse, a second visit was made in order to see the man himself, and, if it was considered necessary, further treatment as an out patient was suggested.

The relatives, of course, felt the strain of readaptation just as the man had done. Some reacted badly, producing additional stress for the patient, and complaining that he had become quieter, or more difficult to please, or that he ate more than his share of the family rations. Others showed remarkable insight into the repatriate's difficulties and gave striking accounts of his progress. Two mothers attributed their understanding of their sons' difficulties to the experience they had gained when their prisoner husbands had returned from the world war 1914–18 in a similar condition.

General Result

The general picture as far as symptoms go was as follows :

Completely recovered	22
Improved	66
Unimproved	12
	100

Those listed as completely recovered declared they were perfectly well, as well as they were before the war. Those unimproved all stated they had got somewhat better during their hospital stay, but had again deteriorated when faced with conditions outside ; 4 of the 12 said they were still better than on admission to hospital, while 8 said they were as ill as at any previous time.

The stresses to which these men were subjected upon discharge were inquired into, and housing and work only will be reported here. Housing was a major cause of trouble in nearly 50 per cent. of the cases ; 38 men were living in definitely overcrowded conditions, and more were likely to do so when their families became fully reunited. In several instances the patient was living with his wife, his parents, and a married sister and her children. Six of the 38 admitted to quarrels with the relatives with whom they were compelled to live. Six others, who were not considered actually overcrowded, were unable to get on with relatives or neighbours living in the same house, and were under considerable emotional stress from this source. In few of these cases did there seem any hope of early relief.

Work Resettlement.—The general situation was as follows :

Pre-war jobs	34
New jobs in old trade ..	18
New trade	40
No work done	8
	100

Of those returned to their pre-war jobs, 27 had decided on this course before coming to hospital, some because of the obligation they felt after having had their pay made up by their firms during their absence, rather than for a particular preference for the work itself. Four others had decided to return after interviewing the D.R.O. in hospital, and 1 who had left hospital with other plans in mind had returned in response to family pressure. Two had returned only temporarily, while waiting for vacancies in Government Training Schemes, and 1 of these felt guilty and unhappy in his job as he alleged older employees were being dismissed in order to make room for the return of service men. In all, 28 of the 34 declared they were satisfactorily settled and happy in their work. It was somewhat difficult to discover just how their present work status compared with their pre-war position, as often the relatives did not know, and, in any case, the men had only been at work for a short period. As far as could be judged 6 had improved in status, and 1, who had abandoned work shortly after starting, for health reasons, had deteriorated. Some of those who had improved appeared to be doing extremely well.

The men who had taken new jobs in their old trade were mostly unskilled men who did not qualify for reinstatement owing to the short period they were in their last pre-war job ; there were a few who preferred to find new jobs despite the possibility of reinstatement. Eleven of the 18 said they were content, and 5 said they were waiting for a chance to improve their status ; 2 had apparently deteriorated.

Of the 40 men who had embarked upon a new trade, 21 said they were contented in it. A further 5 were hoping soon to improve their status—they were waiting for licences to open businesses, or for partners to be demobilized etc.—and 2 of these were attending technical schools. In addition 3 were waiting for government training. The remaining 10 were undecided about their jobs, or were discouraged about them ; 2 of these had had to

abandon work for health reasons and were attending out-patient clinics.

Of the 8 men who had done no work, 1 had been in hospital with infectious hepatitis and 1 was attending a civilian resettlement unit. Of the remaining 6, who presumably had not started for reason of maladjustment of one sort or another, 5 stated they felt much improved, and this statement tallied with the impressions of relative and investigator. Only 1 of them came in the group of 12 unimproved ; 11 of these unimproved men had at least begun work, though some had had to abandon it. Pre-army work history was assessed as satisfactory or the reverse, the latter being characterized by much unemployment, frequent changes in job, or any down-grading of status. Seventeen of our 100 men were classified as having had unsatisfactory pre-war histories, but none of the 6 non-starters were amongst them. All 17 had returned to work promptly.

Thus of the total group of 100, 60 said they were settled and well contented at their work and a further 16 were looking forward to bettering their condition in the near future. On the other hand, 6 men never started work at all for reasons of maladjustment, and 3 abandoned it because of recurrence of their symptoms. This is a very favourable outcome (compare Lewis, 1943), but we are by no means certain it will persist, for the reasons now to be given.

Government Training Schemes.—The Government Training Schemes offered a particularly tempting prospect to the repatriated prisoner of war, and 24 of our 100 men made application while in hospital for one or other of the trades in which training was offered. But three months after discharge only 1 single man was in the training he had applied for. Three others had changed the trade and begun training. Three more waited still for their first choice, and 2 had changed the trade and waited for their second choice. Fifteen men had given it up as a bad job, 12 of these being men now engaged in other jobs, and 3 still out of work. The 5 who still waited to train all showed great keeness to do so and between them had a high degree of neurotic symptoms, which could largely be attributed to their unsettled state.

The investigator felt that the delay in starting the course was a definite factor retarding the recovery of those men who had opted for it. Still more were likely to abandon the idea, though not all those who said they no longer wanted to train had actually cancelled the course, and some might have later returned to it. During their period of daily visits to the labour exchange, the patients said they had been given no encouragement whatsoever ; on the contrary the Exchanges usually encouraged the men to abandon the idea of training or at least to change to some alternative course where the waiting list was shorter.

At the same time, the labour market was very favourable to the neurotic, and a temporary job with good pay was easy to obtain. These were mostly obtained through a friend or casual acquaintance and very many were in the building trade, with local contractors, and had the additional advantage of being near to the patient's home, whereas the government training often took place at a considerable distance from it. In some cases training involved living in hostels, an arrangement peculiarly repugnant to the neurotic repatriate, with his special desire for the security and protection of the home.

The majority of these men, according to the Ministry of Labour D.R.O. and the psychiatrist in charge of them would have proved good material for training. The training scheme must be said to have failed where these men are concerned, and it is likely that their condition will deteriorate should they become redundant on an overcrowded labour market in the future. It is at least a possibility that many who could have become skilled workers will, instead, ultimately become drifters among the permanent unemployed.

Changes of Mind about Work.—A large number of men, 30, had decided against the plans they had made while in hospital. Fifteen of these were those who had been disappointed over their training courses ; the others, in spite of advice received at the hospital, had found quite different work once they had come into contact with the labour market outside.

The explanations given were all very similar. "I had a friend who knew a man . . .", " a local contractor talked to my father", even " the wife's boss said he had a job going." It was always through direct personal contact that the job was arranged, and it was precisely because of the intimate nature of the arrangement that the men responded so eagerly. In one case the man had already been back at his old job and was feeling unable to carry on owing to the noise of the engineering shop, when a casual acquaintance stopped him in the street and offered him work as a joiner in his building firm. Carpentry had always been the man's hobby, and the arrangement proved a very happy one ; the patient recovered his self-confidence and was happy and contented when interviewed.

The majority of jobs obtained in this way were of an unskilled or semi-skilled nature, and though in some cases the change of plan was definitely o

advantage to the patient, it may be that in others his ultimate security will turn out to have been jeopardized.

Work Missed through Illness.—The short-term nature of this follow-up makes no statement about the effect of residual illness on working capacity valid. Actually only 8 men of those who returned to work missed over 14 days during this period, but on discharge from the army these men all got two months leave with pay, and though the majority (59) returned to work before this period expired, some had been at work only a month when visited.

Ministry of Labour Follow-up.—We can to some extent check these results in our sample by reference to a follow-up done by the Ministry of Labour. This consisted of a letter sent to the patient's home three and a half months after his discharge from hospital, and the returns are complete for the six-months period July to December, 1945, only. During this period 687 patients were discharged and 610, or 90 per cent., were reported as being in work or training, 31 not yet in work, and 8 unfit for work. Replies were not received from the patients in 20 cases and from the local employment exchanges in 18. It seems, therefore, that our sample at best does not greatly misrepresent the facts as to the entire group.

General Discussion

From every point of view—clinical findings, physiological results, psychometric tests, and treatment results—these men appear to lie between the normal person and the usual neurotic seen in neurosis centres, and to whom we were accustomed, for example, at Mill Hill Emergency Hospital. Since they were the most sick 1 per cent. of the repatriates, it must follow that the truly neurotically predisposed in the army were either not placed in a position where they were likely to be captured or were unable to survive the rigours of captive life in Germany without dying, or becoming so ill as to be repatriated. As it turned out, our problems had been very similar to those met with in the civilian resettlement units (which were for rehabilitating the non-neurotic repatriate), as we discovered at our first meeting with Wilson (1947) and his associates. It seems that the symptoms of our patients are probably exaggerations of the usual repatriates' reaction, and our previous experience inclines us to believe they are not confined to prisoner-of-war repatriates. Similarly, it follows that the general lines of treatment we found to be effective with our group may with advantage be followed in dealing with the re-entrance of a small outcast group into a large parent one.

It may be remarked in passing that our "semi-neurotics" perhaps show a closer relation to the situation of experimental neurosis in animals than do the classical neuroses. Though it is true that such animals may on occasion show the whole gamut of neurotic behaviour, including compulsive acts, rituals, and regressive behaviour, the more usual manifestations in cat (Masserman, 1943), dog (Gantt, 1943), and sheep (Anderson and Parmenter, 1941) are just those seen in our patients. Disturbances of heart rate and respiration occur (the oxygen uptake of sheep following exercise has yet to be investigated), restlessness, irritability, and distrust and dislike of those responsible, as they think (quite rightly, in the animal's case) for their condition. Some animals, be it noted, become shy and asocial as a result of this treatment, and, in the case of sheep, stay apart from the rest of their flock: were they but human, feelings of repressed guilt (about what, in this case?) would undoubtedly be attributed to them.

As in Masserman's cats, it was the threat of return to the situation of conflicting drives, which had initiated the neurosis, that most upset our patients. The cats showed marked anxiety on being returned to the circumstances in which the neurosis-producing situation had occurred; nothing in our patients caused greater symptoms of anxiety, amounting sometimes to panic, than the idea that they would be returned to army service. They mostly believed, as did Jeffrey and Bradford's (1945–6) patients, that they were to be released from further duty as of right; and it was obvious that, try as they would, they could not but identify the British N.C.O.s (that some had met again for a short time and others only imagined in advance) with their guards, and the army barracks with their prison.

Summary

1. A description is given of the clinical characteristics, treatment, and follow-up results of repatriated prisoners of war from North-west Europe suffering from neurotic symptoms. These men constituted the most maladjusted 1 per cent. of the 100,000 repatriates.

2. A detailed history and symptomatology was recorded for a sample of 100 of the 811 dealt with. The conclusions reached are that these men had much less constitutional predisposition to neurosis than the usual army neurosis centre case. They were also less ill than such cases. The most common and severe symptoms of these men were the following: lack of concentration, depression, feeling of not belonging since repatriation, shyness in the presence of women, asocial behaviour, fatiguability, breathlessness on effort, effort intolerance, trembling,

and resentfulness towards authority, in particular the army.

3. Physiological and psychometric tests, reported elsewhere, entirely support the conclusion that these men are "semi-neurotic" and lie between the normal and the usual neurosis centre patient.

4. Both psychiatrists taking the detailed histories related symptoms of depression mainly to external stress, and somatic symptoms to constitutional predisposition. Such a finding should be considered cautiously in view of other evidence referred to.

5. Treatment is described, with special reference to group methods, work therapy outside the hospital, placement by the resident disablement rehabilitation officer, and the important role of nurses in such a centre.

6. A follow-up study of one hundred patients living in the London area was done by a psychiatric social worker, three to five months after discharge. At this time twenty-two patients were completely recovered, sixty-six improved, and twelve unimproved. Ninety-two had returned to work, and sixty were happy and contented in it. Six had not returned for reasons of maladjustment, and three had stopped working because of symptoms. The type of work the patients returned to, and the efficacy of the Government Training Scheme are discussed. It is concluded that though they are now largely well employed, numbers of these men may become unemployed if labour market conditions become less favourable for them.

To Miss M. Croft, who did the follow-up study, we should like to express our appreciation, and our admiration for her excellent and sensitive work and for the way in which she covered, literally, the ground. We also wish to thank Surgeon-Captain R. G. Henderson, Medical Superintendent of the Southern Hospital, Dartford, for his unfailing co-operation during the existence of our unit.

References

Anderson, O. D., and Parmenter, R. (1941). *Psychosomat. Med. Monographs*, **2**, nos. 3, 4.
Eysenck, H. J. (1947). "Dimensions of Personality." London.
Gantt, W. H. (1943). *Psychosomat. Med. Monographs*, **3**, nos. 3, 4.
Jeffrey, M., and Bradford, E. J. G. (1945–6). *Brit. J. med. Psychol.*, **20**, 422.
Jones, M. (1944). *Amer. J. Psychiat.*, **101**, 292.
——(1946). *Brit. med. J.*, **1**, 533.
Lewis, A. (1943). *Lancet*, **1**, 167.
Masserman, J. H. (1943). "Behaviour and Neurosis." Chicago.
Newman, P. H. (1944). *Brit. med. J.*, **1**, 8.
Tanner, J. M., and Jones, M. (1948). *J. Neurol., Neurosurg., Psychiat.*, **11**, 61
Torrie, A. (1945). *Brit. med. J.*, **2**, 192.
Whiles, W. H. (1945). *Ibid.*, **2**, 697.
Wilson, A. T. M., Doyle, M., and Kelnar, J. (1947). *Lancet*, **1**, 735.

THE PSYCHOLOGICAL SYMPTOMS AND THE PHYSIOLOGICAL RESPONSE TO EXERCISE OF REPATRIATED PRISONERS OF WAR WITH NEUROSIS

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Introduction

The object of this paper is twofold: first, to describe and analyse the symptoms of repatriated prisoners of war who were sent to a neurosis centre for rehabilitation; and second, to report some physiological measurements of these men's response to moderate exercise. These patients are of peculiar interest, in that they represent what might be called a "semi-neurotic" population, of men who have not the degree of predisposition of the usual civilian psychoneurotic, but who have developed mild neurotic symptoms under considerable environmental stress. A general description of their characteristics and of their treatment and its results has been given in the paper at p. 53 of this issue.

The first part of the present paper reports an attempt to quantitate the severity of the various symptoms complained of, and from an analysis of this data to arrive at some classification of this sort of neurosis in symptomatological terms which are at least less arbitrary and less objectionable from the point of view of method than those in current use. It is commonplace that different psychiatrists may on occasion diagnose the same neurotic patient quite differently; one as "reactive depression," another as "anxiety state," a third as "effort syndrome." This happens when a patient has symptoms suggestive of all three of these diagnoses, thus making it impossible for a valid appraisal in one descriptive category only to be arrived at. Believing that such a patient—and indeed, all others—should be classified on a rating of severity in each of several such descriptive categories, we have endeavoured to discover what categories would be most suitable. This part of our study should be regarded as a tentative and pilot one only; but we believe that interesting results might be obtained by applying this method to more classical cases of neurosis, by spending more time on detailed symptom study, and, primarily and of most importance, by studying further the pathological physiology of such patients.

One aspect of this pathological physiology is the response to exercise, and the second part of our study reports measurements on these prisoner-of-war patients similar to those previously made by one of us on the more usual cases of neurosis (Jones and Mellersh, 1946 a, b).

Material

The material consisted of 100 soldiers, who were a sample, selected by taking every fifth admission, of the patients at the ex-prisoner-of-war neurosis unit (excluding the very occasional mental defective and psychotic). They were examined during the period June to September, 1945. These men had all been prisoners of war in Germany for varying lengths of time, and on repatriation, or return to their unit after their repatriation leave, had shown signs of psychological maladjustment. Specifically, they constituted the most maladjusted 1 per cent. of all prisoners of war returned from north-west Europe. Nevertheless, as we have indicated, they cannot be classed as psychoneurotic in the usual sense, as applied to civilian patients. They are far less constitutionally predisposed to neurosis than the usual patient, and clinically, physiologically, and psychologically appear to lie between the normal and the "true" neurotic. The mean age of the 100 was 27·3 years, with a standard deviation of 4·0 years. Excluding eight old soldiers, the average time of army service was five and a half years with a S.D. of one year. An average of four years had been spent overseas, and three and a half years as prisoners of war.

Psychological Symptoms

Methods.—Fifty of these patients were seen by investigator J, and fifty by investigator T. Throughout this section these two groups will be considered separately. Difference in results for the two groups spring mainly from the investigators, for no significant differences exist between the subjects in age, time of service and of imprisonment, physique, oxygen consumption following a standard exercise, and other physiological tests. Despite an alternating method of selection, however, J's subjects were more intelligent than T's, both by progressive matrices test ($P < 0.01$) and Mill Hill Vocabulary ($P = 0.06$). In this regard, T's subjects are similar to normal conscripts as reported by Eysenck (1947), while J's are superior to them.

In an interview, lasting usually from two to two and a half hours, a detailed history was taken following the usual practice for neurotic patients, but using a stereotyped case form. Inquiry was made about the 64 symptoms shown in Table I, and an attempt was made to obtain more information than simply absence or presence of a particular symptom. The apparent severity of each symptom was rated on a seven-point, equal-appearing interval scale, 1 representing absence, 2 minimal severity, 7 maximal severity. Finally, when the history was completed, the investigator made his diagnostic summing-up of the case in a similar manner. Since we considered that neurotic patients without hysteria could not be satisfactorily separated into a dichotomy of reactive depressions and anxiety states, but could show symptoms of each at the same time, we made ratings under the three headings: (A) somatic anxiety (anxiety with somatic symptoms predominating); (B) psychic anxiety (left loosely defined, for later examination, but representing roughly anxiety without somatic response); and (C) depression. Ratings were also made under headings of hysteria, conversion, dysmnesic and dramatization, psychopathic character, paranoid symptoms, schizophrenic symptoms, and hypomanic symptoms. These latter ratings are not reproduced since they assumed no importance; their average figures were all under 1·4, and we had no individuals whose clinical diagnosis was hysteria or psychosis.

Some symptoms lend themselves readily to ratings of this sort; others do not. Sweating, palpitation, and effort intolerance, for example, can be readily, if roughly, quantitated; such symptoms as feeling "U.K. morals worse" cannot. Most of the symptoms, such as asocial, lack of confidence, or short-tempered, lie between these extremes. Careful inquiry into the details of a symptom, however, usually leads to some considerable basis for judgments of this sort; the rater of asocial, for instance, inquires precisely what stimulus was necessary to get the patient to meet strangers, friends, and close relatives over the last two months. In general both intensity and duration of a symptom were taken into account, more weight being given to the former.

Table I shows the average ratings made by each investigator. In general, there is very good agreement between J and T as to which symptoms were the most marked in these patients; the ratings were made entirely independently, and, after initially discussing the

TABLE I

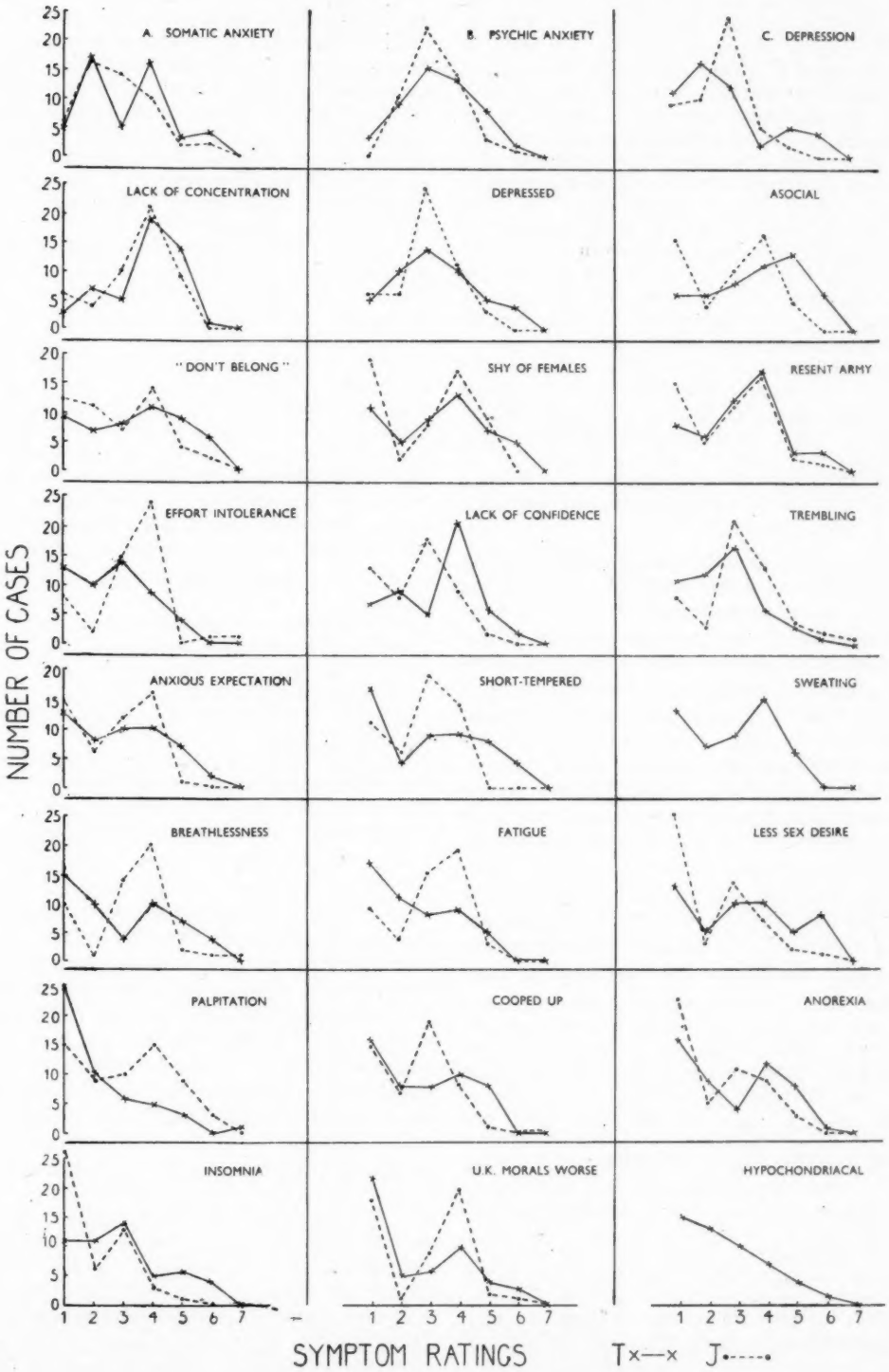
AVERAGE RATINGS OF SYMPTOMS BY J AND T: 50 PATIENTS EACH

	J	T
Somatic anxiety	2·84 σ 1·2	3·14 σ 1·4
Psychic anxiety	3·26 0·9	3·40 1·2
Depression	2·62 1·0	2·64 1·4
I. *Symptoms with average rating above 2·50 by both J and T*		
Lack concentration	3·5	3·7
Depressed	3·0	3·3
Asocial	2·8	3·7
Don't belong	2·9	3·4
Shy females	2·7	3·3
Resentful army	2·8	3·2
Effort intolerance	3·3	2·6
Lack confidence	2·6	3·4
Trembling	3·0	2·6
Anxious expectation	2·6	2·9
Short tempered	2·7	3·0
Sweating	*—	2·9
II. *Rating above 2·0 by both J and T*		
Breathlessness	3·2	2·5
Fatigue	3·1	2·5
U.K. morals worse	2·8	2·5
Cooped up	2·5	2·7
Less sex desire	2·3	3·2
Anorexia	2·3	2·8
Palpitation	2·9	2·1
III. *Rating above 1·5 by both or above 2·0 by one*		
Dizziness	2·3	2·0
Throbbing headache	2·2	1·8
Fear fail civil life	2·0	2·7
Insomnia	1·9	2·9
Effort phobia	1·7	2·4
Pressure headache	1·5	2·9
Hypochondriacal	1·4	2·5
Nausea	1·5	2·4
Hot flushes	1·7	1·6
Chest constriction	1·6	1·6
Dry mouth	2·1	1·2
Guilt feeling	1·3	2·2
Nightmares	1·4	2·1

* Not rated by J.

Other symptoms rated

Throbbings in neck, syncope, hyperventilation, tetany, stammering, abdominal cramps, frequency, enuresis, left chest pain, vomiting, flatulence, diarrhœa, fear of impotence, impotence, fear of sterility, family's affection less, patient's affection less, phobias, P.o.W. dreams, battle dreams, weeping, suicidal ideas, suicidal intentions, depersonalization, paranoid, obsessive-compulsive, sensation plus, sensation minus, motor weakness, dysmnesic, hysterical fits, resent civil population.



FIGURE—Distributions of ratings for traits analysed.

definition of symptoms, the two investigators did not at any time compare notes or discuss cases, formally or informally. Thus a comparison of the two series of results is a measure of the reliability of the ratings, akin to that obtained by the split-halves or odds-and-evens methods. The chief symptoms can be seen from the Table, and also those which these patients were usually lacking. It is with the commoner symptoms that nearly all the remainder of this section is concerned; the ratings of these were all intercorrelated for each observer, and the resulting matrices factor-analysed.*

The criterion for including symptoms in this analysis was, for T, those symptoms in which less than 20 men rated 1. These comprise all of groups I and II (Table I), except for less sex desire and palpitation, and include also insomnia, headache, and hypochondriacal of group III. The intercorrelated symptoms of J are the same, with inclusion of palpitation and U.K. morals worse and the omission of headache, hypochondriacal, and sweating. These are likewise symptoms in which fewer than 20 men rated 1, with the 3 exceptions of anorexia, U.K. morals worse, and insomnia. Somatic anxiety, psychic anxiety, and depression, the diagnostic traits, were included in each analysis.

In the Figure the distribution of these symptom ratings for each investigator is shown. Most of the distributions are of single-humped type, apart from the 1 ratings, though some of the less severe and less frequent ones, shown towards the bottom of the figure, begin to approach the J-shaped curve of the really rare trait. T tended to spread his ratings somewhat more than did J, but in general the distributions of the two investigators are fairly similar. As might be expected, the reliability of the commoner traits is somewhat greater than that of the rarer ones; the ranks correlation coefficient between the two distributions ranges from 0·46 to 0·95, with the average for the top nine traits in the figure being 0·84, and for the remainder 0·76. The average for the entire group of traits included in the factor analyses is 0·79, which seems reasonably satisfactory.

Thirty-four of the intercorrelations, chosen at random, were plotted out, and no marked curvilinearity of regression was visible to the eye. Within the broad limits of our accuracy, then, the product-moment coefficient can be taken to represent the degree of association between pairs of symptoms—with one reservation. We are disturbed by the piling up of 1 ratings. In very many cases, the single-humped curve is ranged between 2 and 7, simply because these ratings represent degrees of intensity of a symptom which is *present*. The rating 1 represents *absence*. There is a gap between the ratings 1 and 2 which is not subject to the same scale operation as the intervals of 2 to 3, 3 to 4, and so on. It may be—and this we had in mind in devising the scales—that the rating 1, in palpitation say, really represents the entire scale of unusual heart action from average function to the point where the subject is conscious of palpitation. It might be said that a threshold exists between ratings 1 and 2, and that the trait we are really trying to measure continues to fall in several steps to the left of rating 2; our methods do not enable us to distinguish these steps, and consequently our 1 ratings appear to be excessive in number. With some of the more physiologically-based symptoms this seems a reasonable view to take, but we would be hard put to it to say what precisely such subclinical resentfulness towards army represents. However, since we see no simple way of getting around this difficulty without losing some of our information, we must remain content to draw attention to it. It seems unlikely to have appreciably affected the results of our factor analysis, since the symptoms which show most markedly this bimodality share no position in common in our result.

The two correlation matrices are not reproduced here. The P=0·05 level of significance can be assessed only for the null hypothesis for data not known to be drawn from a population distributed normally, the standard error of r when the true correlation is zero being given by $\frac{1}{\sqrt{N-1}}$. For fifty subjects a correlation of over 0·2 will be considered significant, and the number of correlations greater than this was 47 out of 253 for T, and 73 out of 231 for J. There were no negative correlations significantly greater than zero. The coefficients were calculated by the product-moment method, without grouping. The matrices were then factor-analysed by both bipolar and group factor methods of Burt (1940); the figures in the leading diagonal were determined by an iterative procedure, and simple rather than weighted summation was used.

Results

ANALYSIS OF SYMPTOMS.—The factor analysis solution is shown in Tables II and III. A general and a bipolar (2 group) factor emerge for both investigators, and a small second bipolar factor for T.† About 40 per cent. of the total variance is accounted for by these factors. The general factor is given more prominence by J than by T, and, to a lesser extent, the reverse is true of the first bipolar factor. This general factor has its highest saturations with lack of concentration, shy of females, fatigue, less sex desire, anxious expectation, and the

* Factor analysis is a statistical technique for classifying complex data into more simple terms. In this case, the object is to replace the lengthy description of a patient as "so much in symptoms a, b, c, d, e, f, . . ." by the more concise "so much factor A plus so much factor B plus so much factor C." The factors (obtained by the present method) are independent of each other, while the symptoms are not.

† The factors resulting from this type of analysis are (1) a general factor, which represents those attributes common to every symptom in the data, (2) bipolar or group factors, which represent attributes common to some but not all of the symptoms, and (3) specific factors which are peculiar to a single symptom. As Burt has pointed out, these are merely the old classificatory principles, genus, species, and proprius, of the logicians. The saturation of a factor with a symptom represents the degree of correlation of the trait with the factor, in a way exactly similar to the ordinary correlation coefficient. Thus the score in the general factor represents the answer to a question such as "How much of the features common to all cases of blankitis does X have?", and the score in the bipolar factor answers the question, "Now entirely, apart from blankitis, does X incline more to the thin or the stout side, and how much?"

diagnostic rating, psychic anxiety. J also gave the rating somatic anxiety a fairly high saturation here, but T did not. Presumably this general factor can be taken to represent the common features of psychological maladjustment as shown by repatriated prisoners of war.

The chief bipolar factor has very similar saturations in each set of data. The main positive loadings are effort intolerance, breathlessness, palpitation, and the diagnosis, somatic anxiety. The main negative loadings are depressed, asocial, shy of females, don't belong, and the diagnosis, depression. The group factors 1 and 2 correspond to this bipolar factor. Obviously this factor serves to classify patients on a scale we might call effort syndrome *versus* depressed/withdrawn. On T's second bipolar factor little stress should be laid, since it is entirely absent in J's data. Its saturations do, however, achieve significance according to Burt's criterion (Burt and Banks, 1947) and appear to make sense, being resentment, cooped up, anorexia and headache, *versus* don't belong, lack of confidence, and asocial.

The interpretation of these findings seems to lie clearly with one of two alternatives. Possibly the results reflect merely the prejudices of the investigators, who were admittedly particularly interested in effort syndrome, and who might be imagined (though with difficulty) to have grown such very similar prejudices over a previous 6 months of working together. If this explanation is discounted, then effort syndrome and depressed/withdrawn reaction are two independent ways in which men with little predisposition to the classifical types of psychoneurosis may react to circumstances which they can neither tolerate nor alter. Such a view is neither startling nor new, and accords well with the current conceptions of effort syndrome as a neurotic reaction, and with experience of minor neuroses in army and civilian practice.

The scheme of diagnosing under the three headings somatic anxiety, psychic anxiety, and depression seems to have been fairly well justified. Both investigators used somatic anxiety primarily to designate effort syndrome, though J did not disentangle his rating enough from the general factor. J has, however, expressed his general factor very clearly in the diagnosis of psychic anxiety, which for him is independent of the bipolar factor. T's psychic anxiety diagnosis was a mixture of general factor (which did predominate) and depression/withdrawal. The diagnosis depression represented well the depression/withdrawal symptoms, though it also, for J, was contaminated slightly with general factor. Some such scheme of symptom diagnosis may prove useful in the study of neurotic reactions, at least until more fundamental work on the genesis of these reactions and their physiological bases is forthcoming. It would certainly be desirable to see if non-hysterical neurotics not distinguished from the usual patient by being subjected to the particular stress of prisoner-of-war life could be usefully summed up under the headings general anxiety rating, effort syndrome rating, depression/withdrawal rating.

It will be seen in Tables II and III that some of the symptoms have very low communalities. This means that our classification has left them out of account; that they are largely independent of our factors, and of each other. For this reason they are of considerable interest. Anorexia, insomnia, trembling (which is only slightly allied with effort syndrome) are in this category; so are less sex desire, shortness of temper, resentfulness, and a feeling of being cooped up. These symptoms do not depend on the general severity of the patient's condition, nor on his degree of effort syndrome or depression, and emphatically demand further investigation.

Relation of Symptoms to Environmental Stress and Physical Constitution.—The bipolar factor being unearthed, the question immediately arises as to what makes a man gravitate to one end or the other of it. Can a man react to psychological stress with a well-marked effort syndrome at one time in his life, and an asocial depression at another? Are the factors governing his reaction chiefly genetic and constitutional or chiefly environmental? This question we shall now attempt—quite unsuccessfully—to answer.

Every individual's score in the general and the bipolar factor was worked out from the estimation equations below. The multiple correlations (R) of the estimates with the factor are also given.

General factor (T)=0·5 lack concentration+0·2 shy females+0·2 fatigue−2·8 (R=0·76)

General factor (J)=0·9 psychic anx.+0·1 somatic anx.−3·2 (R=0·79)

Bipolar factor (T)=0·6 effort intolerance−0·4 depressed−0·3 (R=0·92)

Bipolar factor (J)=0·4 som. anx.+0·3 effort intol. −0·6 depression −0·3 shy females −0·1 (R=0·93)

Environmental Relations.—These factor estimates were then correlated with the ratings for various items in the history of each individual; the rating and discussion of these items will be found in the paper at p. 53 of this issue. No significant relation could be discovered with early-environment-adverse rating, total time of captivity, rating of physical health while in captivity, or age. A consistently

positive relation between the prisoner-of-war camp stress rating and the general factor was found, the coefficients being +0·27 for J and +0·17 for T, which, taken together, are significant at the 0·05 level. They are small though reasonable, and may, of course, represent purely a halo effect on the part of the investigators.

Constitutional Relations.—The physique of 89 of these 100 men was investigated by the method of Sheldon (1940). Somatotyping was done anthroposcopically from the usual three pictures, with reference in the majority of cases to the Ht-Wt index at age 18. The measurements recommended by Sheldon were taken, and will be reported later, but nearly all our men were above the age range of Sheldon's tables. The somatotyping of all the men was done by one of the investigators, who had had special training in this procedure.

No relation could be demonstrated between the general factor score and somatotype, but equivocal results were obtained for the bipolar factor. For J's subjects, the correlations of endomorphy, mesomorphy, and ectomorphy, and this factor were all insignificantly low. For T's subjects, however, they were respectively +0·37, −0·36, and +0·19, the first two being significant. This might be dismissed as prejudice, were it not that T's conscious predilections, at least, were quite in another direction, in favour of the third figure being the high one. More of the total symptom variance enters into T's bipolar factor than into J's and this might be taken as supporting the repeatability of T's figures. Future work must decide the question, but the suspicion, at any rate, is raised that the more mesomorphic people become depressed and asocial under stress rather than short of breath, and that both increasing endomorphy and ectomorphy predispose in the other direction. (The partial correlation of endomorphy and the bipolar factor with ectomorphy held constant is 0·47, and of ectomorphy and the bipolar factor with endomorphy held constant 0·34.) The correlations between somatotype and the symptoms effort intolerance and shortness of breath support this idea. J's subjects did have negative correlations between these symptoms and mesomorphy, of −0·19 and −0·25, but, taken in isolation, these could be merely due to chance. The equivalent correlations for T were −0·25 and −0·17. J's data also showed a

TABLE II

BIPOLAR FACTOR SATURATIONS

Symptom	Bipolar (i)		Bipolar (ii)	General		Communality	
	T	J	T	T	J	T	J
Effort intolerance	0·77	0·63	−0·20	0·55	0·66	0·94	0·83
Breathlessness	0·72	0·46	−0·16	0·37	0·63	0·68	0·61
Somatic anxiety	0·59	0·42	+0·13	0·24	0·74	0·42	0·72
Palpitation	—	0·35	—	—	0·53	—	0·40
Trembling	0·29	0·10	−0·21	0·06	0·31	0·13	0·11
Insomnia	0·19	0·10	−0·06	0·21	0·37	0·08	0·15
Less sex desire	0·16	−0·12	+0·08	0·37	0·44	0·17	0·21
Headache	0·16	—	+0·41	0·43	—	0·38	—
Sweating	0·13	—	−0·08	0·41	—	0·19	—
Fatigue	0·12	0·26	−0·14	0·51	0·56	0·28	0·38
U.K. morals worse	—	0·18	—	—	0·32	—	0·13
Hypochondriacal	0·09	—	+0·39	0·44	—	0·36	—
Lack of concentration	−0·05	−0·15	+0·21	0·59	0·44	0·39	0·22
Cooped up	−0·08	−0·33	+0·42	0·22	0·17	0·23	0·14
Short-tempered	−0·13	−0·01	+0·27	0·28	0·40	0·17	0·16
Don't belong	−0·16	−0·40	−0·43	0·41	0·62	0·38	0·54
Resent army	−0·17	+0·19	+0·53	0·05	0·29	0·31	0·12
Anxious expectation	−0·17	+0·22	−0·23	0·45	0·61	0·28	0·42
Lack confidence	−0·18	−0·15	−0·29	0·48	0·28	0·35	0·10
Shy females	−0·24	−0·43	−0·04	0·64	0·52	0·47	0·46
Anorexia	−0·25	−0·01	+0·44	0·20	0·42	0·30	0·18
Psychic anxiety	−0·39	−0·06	−0·27	0·56	0·77	0·53	0·60
Depression	−0·39	−0·52	−0·25	0·35	0·56	0·34	0·58
Asocial	−0·41	−0·38	−0·27	0·46	0·64	0·45	0·55
Depressed	−0·61	−0·33	−0·22	0·47	0·50	0·64	0·36
Contribution to variance	12%	10%	8%	17%	26%	37%	36%

significant relation of these symptoms to ectomorphy (+0·20 and +0·30), which T's did not. T, on the contrary, obtained the significant figures with endomorphy of +0·31 and +0·32. On the other end of the factor, T's figures for asocial and depression are, endomorphy −0·29 and 0·00, mesomorphy +0·23 and +0·23. J has no significant correlations here, and neither investigator has significant correlations between somatotype and shy of females or lacks confidence.

Since endomorphy and ectomorphy are positively correlated and mesomorphy negatively correlated with the femininity component of male physique (Sheldon, 1942), it is possible that the relation may be with this component rather than with the somatotype components *per se*. Such a relation would be indicated by the pathological physiology of effort syndrome (Tanner, 1948a), but, as we have been unable to demonstrate that exercise response itself in these patients is related to the bipolar symptom factor, we must leave this matter undecided.

The somatotype components are independent of gross body size. The factor analysis classification of physique, however, leads to an expression for body size in the form of a regression equation involving height, weight, and leg length (Burt, personal communication). We did not have the last of these available, but it has been shown that, in fifty students, the Du Bois surface area expression correlated with the size factor regression estimate to the extent of 0·99 (Tanner, 1948b). Consequently surface area was used as a measure of gross size.

Neither factor estimate showed a significant relation with body size. The general factor correlated −0·21 for both J and T, and this might be considered suggestive, particularly in view of Eysenck's finding (1947) that men of small size, or microsomatics, have more adverse symptoms attributed to them by their psychiatrists than do macrosomatics. The bipolar factor estimate correlated −0·19 and −0·24 for J and T; again insignificant, though possibly suggestive that larger people gravitate towards depression rather than effort syndrome.

Neither the rating of constitutional predisposition nor the progressive matrices score was found to correlate with either general or bipolar factor.

Physiological Response to Exercise

Sixty-five of the hundred men (40 of J's series and 25 of T's) were subjected to a standardized exercise tolerance test on a bicycle ergometer in the way previously described (Jones and Mellersh, 1946a). The subject

TABLE III

GROUP FACTOR SATURATIONS

Symptom	General		Group 1		Group 2		Group 3	Communality	
	T	J	T	J	T	J	T	T	J
Lack concentration	0·76	0·43	—	0·21	—	—	—	0·58	0·23
Shy females	0·56	0·35	0·47	0·63	—	—	—	0·53	0·52
Fatigue	0·55	0·49	0·24	—	—	0·38	—	0·36	0·38
Less sex desire	0·51	0·48	—	—	—	—	—	0·26	0·23
Hypochondriacal	0·50	—	—	—	—	—	0·26	0·32	—
Anxious expectation	0·46	0·58	0·24	—	—	0·26	—	0·27	0·40
Psychic anxiety	0·46	0·87	0·43	—	—	—	—	0·40	0·76
Headache	0·45	—	—	—	—	—	0·35	0·33	—
Sweating	0·40	—	—	—	0·39	—	—	0·31	—
Palpitation	—	0·43	—	—	—	0·43	—	—	0·37
Effort intolerance	0·24	0·39	—	—	0·86	0·88	—	0·80	0·93
Don't belong	0·22	0·49	0·47	0·57	—	—	—	0·27	0·57
Short-tempered	0·21	0·46	—	—	—	—	0·33	0·15	0·21
Lack confidence	0·20	0·21	0·65	0·24	—	—	—	0·46	0·10
Insomnia	0·19	0·32	—	—	0·19	0·21	—	0·07	0·15
Depressed	0·13	0·40	0·66	0·44	—	—	—	0·45	0·26
U.K. morals worse	—	0·27	—	—	—	—	—	—	0·13
Cooped up	0·08	0·00	—	—	—	—	0·48	0·24	0·21
Anorexia	0·07	0·45	—	—	—	—	0·47	0·23	0·20
Breathless	0·05	0·48	—	—	0·90	0·60	—	0·81	0·59
Asocial	0·02	0·53	0·89	0·54	—	—	—	0·79	0·57
Somatic anxiety	0·00	0·62	—	—	0·63	0·60	—	0·40	0·74
Depression	−0·04	0·38	0·61	0·70	—	—	—	0·37	0·48
Trembling	−0·07	0·32	—	—	0·33	—	—	0·11	0·10
Resent army	−0·24	0·23	—	—	—	0·25	0·90	0·87	0·12
Contribution to variance	12%	20%	12%	8%	10%	9%	7%	41%	38%

bicycled at forty-two revolutions per minute for five minutes, doing approximately 930 kg.m./min. work against friction. Unfortunately the time between admission to hospital and the test could not be made completely uniform for each man, but it was about two weeks in most cases. Some degree of symptomatic recovery had occurred by this time, but by no means as much as was finally recorded. Resting pulse rate after twenty minutes' rest before exercise was recorded ; and, during the first five minutes after exercise had ceased, total ventilation, respiratory rate, oxygen consumption, oxygen equivalent (the volume of air breathed for the assimilation of 100 ml. of oxygen) and pulse area. The last expression measures the rapidity with which the heart rate returns to the resting value, and is the number of heart beats during the first four minutes post exercise, plus the mean heart rate during the eighth, ninth, and tenth minute post exercise, and minus five times the resting rate.

Table IV compares the physiological measurements during the recovery from exercise of the present patients, 20 normal controls, and 47 patients with well-marked effort syndromes or anxiety states. The controls and the 47 effort-syndrome-anxiety states have been reported previously (Jones and Mellersh, 1946b) ; the controls were somewhat unathletic soldiers of approximately the same age and weight range as the neurotics. The 20 patients in the last row of Table IV are 20 of the 47 men of the row above. It will be seen that the neurotics have a larger oxygen consumption than the controls ($P < 0.01$), a larger pulse area ($P < 0.01$), a greater ventilation, mainly because of greater respiratory rate, and higher oxygen equivalent, signifying a ventilation in excess of that needed to supply the oxygen requirement. In all these measurements, the present prisoner-of-war patients lie between the neurotics and the normals. Though the mean oxygen consumption of the prisoners of war does not differ from that of the controls, the hypothesis that both are samples from the same, healthy population is untenable, for a significant difference ($P < 0.01$) exists between the standard deviations of the two series. The prisoners of war, in their greater scatter, are half way to the neurotic figure. The pulse area mean of the prisoners of war lies in between the neurotic and the control figures, and is significantly different ($P < 0.01$) from either of them. In total ventilation, respiratory rate, and oxygen equivalent the prisoners of war fall between the other two groups.

The interpretation of the neurotics' poor response to submaximal exercise is not yet perfectly clear. The subject is to be reviewed elsewhere (Tanner, 1948a). It is thought very probable that in the neurotic excessive anærobic muscular contraction takes place at the beginning of exercise, and the suggestion has been put forward that this is due to an initially insufficient dilatation of the muscular vessels. It has been shown that the response is worse in chronic lifelong effort syndrome cases than in acute ones (Jones and Scarisbrick, 1946 ; Cohen, and others, 1947) and the question arises as to whether our prisoner-of-war figures coincide with those for the acute effort syndrome or anxiety state, without constitutional predisposition, or whether they are still closer to normal. This cannot be dogmatically answered from the figures available, but it does seem that both oxygen consumption and pulse area of the prisoners of war are somewhat less than for the acute anxiety states. The physiological studies, then, lead us to the conclusion that the prisoners of war are men with little or no constitutional predisposition to neurosis, and are suffering from a rather milder attack of anxiety than the usual army patient referred to a neurosis centre with a short history of illness. This conclusion fits exactly with our clinical impression and

TABLE IV

COMPARISON OF FIVE-MINUTE POST-EXERCISE MEASUREMENTS OF NORMALS, EX-PRISONERS OF WAR, AND ANXIETY STATES

	5 min. recovery oxygen consumption ml/min.		Pulse area		Ventilation l/min.	Respiratory rate per min.	Oxygen equivalent	Volume per breath ml.
	Mn.	S.D.	Mn.	S.D.				
20 normal	586	35·9	86	35·8	17·0	18	2·9	929
65 ex-P.o.W.	589	60·5	122	38·8	21·4	24	3·6	1,092
47 effort syndrome plus anxiety state ..	693	91·6	145	40·5	—	—	—	—
20 effort syndrome plus anxiety state ..	—		—		28·3	28	3·9	985

with the psychometric results (psychological questionaire, body sway suggestibility, dark vision). (Eysenck, 1947, p. 255.)

Relation of Physiological Measurements and Psychological Symptoms

The estimates of the general and bipolar factors were then correlated with these physiological measurements. For the general factor, the only significant relation was with oxygen equivalent, the coefficient being +0·25 (P=0·05). Though the other measurements will successfully differentiate degrees of neuroticism in a heterogeneous population, oxygen equivalent appears to be the only measurement sensitive enough to reflect the severity of the anxiety within our homogeneous group. Our estimate of severity is, of course, a very imperfect one, and perhaps better quantitation in this direction, rather than in the physiological tests, is what is needed.

No significant relations distinguishing effort syndrome from depression/withdrawal were found. This result agrees with earlier findings on the inseparability by exercise response of effort syndrome cases and anxiety states in general. Poor effort response is by no means confined to patients who complain of it ; it is a general characteristic of all neurotic patients except those with conversion hysteria.

The Relations of Physiological Measurements and Physique

Size Factor.—For the sixty-five subjects, the correlation coefficient of surface area with oxygen consumption was +0·31, and with pulse area −0·40 ; with resting heart rate and oxygen equivalent, insignificantly low. Oxygen consumption during moderate exercise, at any rate in the normal, is more highly correlated with size than this (Seltzer, 1940) while total recovery oxygen after slight to moderate work is independent of body weight (Berg, 1947). The latter result comes about because the speed of recovery is faster for those who at the start of recovery have a higher oxygen consumption. It thus seems probable that our relationship of 0·31 reflects our 5-minute oxygen collection : had we collected for less time, it would have been greater, and for more time, less. In comparing two groups, allowance should obviously be made for this size relation unless the time of collection is extended, say, to 7 or 8 minutes, sufficiently to reduce the correlation to insignificant levels. In the present data the regression of oxygen consumption on body weight is only 0·9 ml./min. per lb. however, and adjustment makes no difference to our conclusions, the difference in weight of controls and prisoners of war being 5 lb. only, in favour of the latter. The same thing applies to pulse area ; comparisons should be made with the size factor adjusted, though in the present instance the results are essentially unchanged.

Somatotype Component.—Only one significant relation was found between the somatotype components taken singly and oxygen consumption, pulse area, and oxygen equivalent. This was a correlation of 0·32 between endomorphy and oxygen equivalent, indicating that the higher the fat component, the less the efficiency of respiration following exercise. This relation is independent of the relation of oxygen equivalent to the general symptom factor, and presumably relates to a constitutional difference in exercise response, independent of any neurotic symptoms. Cureton and his associates (1945) found that performance in long-distance running was adversely affected by increasing endomorphy. Whether these relations mirror the masculine-feminine component of build, or endomorphy *per se*, is not yet clear ; in our material the oxygen equivalent had no relation with the shoulder-width/hip-width ratio.

Particular interest attaches to the oxygen consumption figure, since Seltzer has reported that at rest and during moderate exercise linear people have larger consumptions than more lateral individuals of the same gross size (1940). It has been mentioned elsewhere, however, that Seltzer's conclusions do not necessarily follow from the figures he presents, and that his results may be explained entirely by the spurious correlation between indices introduced by his method of handling his data (Tanner, 1948c). All the same, the idea that thin people have a higher oxygen consumption than thick people is an old one (Harris and Benedict, 1919), and very indirect support for it may perhaps be found in the correlation of oral temperature and ectomorphy (Tanner, 1947). Since our data for recovery oxygen consumption reflect only slightly the consumption during exercise, we can throw no direct light on this problem. It seems worth while mentioning, however, that in T's series of subjects, though not in J's a positive correlation of oxygen uptake and ectomorphy was observed, reaching precisely the 0·05 level of significance, with the surface area effect partialled out. Though certainly no conclusion should be drawn from our figures, there does seem to be a strong case for reinvestigating this subject, both in normals and neurotics, during exercise and after it.

Discussion

The differentiation of neurotic patients into hysterics and dysthymics has recently been sum-

marized and discussed by Eysenck (1947). In this classification, all our patients were dysthymics, and what we have attempted is really a further splitting of this group into effort syndrome and depressed/withdrawal reaction. The effort syndrome end of this bipolar factor of ours is clearly visible at one pole of Eysenck's third factor, though depression does not appear there. It is interesting that the symptoms trembling and irritability, or their equivalents, had insignificantly low saturations in Eysenck's third factor and likewise in our bipolar ; dyspepsia correlated with effort syndrome symptoms in his data, however, while anorexia did not in ours. While morphological and physiological differences can be shown to exist between hysterics and dysthymics, we were unable, at least in our small sample and with limited tests, to find surely significant differences between effort syndrome and depression/withdrawal. A morphological difference, with mesomorphs becoming depressed, and ectomorphy and endomorphy increasing the chances of effort syndrome, is suggested but by no means established by this study.

It may be that these two ways of reacting to stress do not differ so fundamentally as the hysteric and dysthymic syndromes : but only studies showing whether a second breakdown is as often the opposite as the same in symptomatology can throw light on this, and, in any case, further physiological tests both of constitutional and reactive functions are obviously indicated.

It does not seem probable that our general factor is equivalent to Eysenck's personality organization (P) factor. There is no correlation between our ratings of constitutional predisposition and our general factor score, whereas the psychiatrists rating, " badly organized personality," had a saturation of 0·92 in P in the Mill Hill study. Rather, the general factor may be regarded as an estimate of the severity of the maladjustment peculiar to returned prisoners of war. It would be interesting to see if the factor were present to a lesser extent in repatriated prisoners of war and other repatriates who suffered no overt breakdown : general experience of such people suggests that this may be the case. If so, this factor may have wider implication, and represent the common reaction upon return of persons who have been separated from their social group.

Summary

1. One hundred soldiers, repatriated prisoners of war from North-west Europe who had been sent to a neurosis rehabilitation unit, were examined by two psychiatrists, fifty men by each. Sixty-four possible symptoms were inquired into in detail, and the severity of each rated on a seven-point scale. Three diagnostic categories, somatic anxiety, psychic anxiety, and depression were also rated. There were no hysterics in the sample. Twenty-two of the symptoms were relatively common, and the scores in these and in the three diagnoses were intercorrelated separately for each observer. The correlation matrices were then factor-analysed, and yielded a general factor and a chief bipolar factor. The saturations for the two investigators agreed well. The general factor represents the syndrome peculiar to returned prisoners of war : it is suggested that such a syndrome, in less severe form, may be characteristic of all expatriates upon return to their parent social group. The bipolar factor represents effort syndrome versus depression/withdrawal reaction. The diagnostic categories were found to describe fairly well effort syndrome group, general factor, and depression/withdrawal group respectively, and the suggestion is made that descriptive diagnoses of non-hysterical neurotics should be couched in something like these terms.

2. Factor scores were estimated, and the relations of factor score to various ratings of environmental stress and to constitution and physique were examined, in an effort to see which influenced chiefly the type of neurotic symptoms. The effort was largely unsuccessful, and few conclusions could be drawn. It appears, however, that patients high in mesomorphy may tend to become depressed rather than to have effort syndrome. Both increasing ectomorphy and endomorphy enlarge the chances of getting effort syndrome ; the relation may be primarily with the masculine-feminine component of physique.

3. Sixty-five of these hundred men underwent a standard exercise test on a bicycle ergometer. Figures for resting pulse rate and for post-exercise oxygen consumption, pulse area, oxygen equivalent, ventilation, and respiratory rate are reported, and compared with those of normal controls and of the usual hospitalized army anxiety-state patients. In every measured characteristic, the repatriated prisoners of war were found to lie between the other two groups, and this is taken as evidence that the prisoners of war were little predisposed to anxiety, and only mildly affected by it.

4. There was a significant positive relationship between the general symptom factor and oxygen equivalent, that is, the amount of air ventilated for the assimilation of 100 ml. oxygen. No significant relations distinguishing effort syndrome from depressed/withdrawal were found ; poor effort response characterizes all neurotics except those with conversion hysteria, and is not, in this mildly ill group, demonstrably worse in those who complain primarily of it.

We wish to thank Surgeon-Capt. R. G. Henderson, medical superintendent of the Southern Hospital, for his co-operation during this study; Sir Cyril Burt for his ready advice and help; Mrs. M. Musgrave for her technical assistance; and Mr. G. W. Bell, Mr. A. C. Hardy, and Mr. J. Prior for help with the computations. One of us wishes to thank Professor W. Le Gros Clark for the use of the facilities of the Department of Human Anatomy, Oxford, where part of the final analysis of the data was done; the other to acknowledge a grant from the Medical Research Council.

References

Berg, W. E. (1947). *Amer. J. Physiol.*, **149**, 597.

Burt, C. (1940). "Factors of the Mind." London.

——, and Banks, C. (1947). *Ann. Eugenics*, **13**, 238.

Cohen, M. E., Consolazio, F., and Johnson, R. E. (1947). *J. clin. Invest.*, **26**, 339.

Cureton, T. K., Hoffman, W. J., Welser, L., Kireilis, R. W., and Latham, D. E. (1945). *Monographs: Soc. Res. Child Development*, **10**, No. 1.

Eysenck, H. J. (1947). "Dimensions of Personality." London.

Harris, J. A., and Benedict, F. G. (1919). *Carnegie Inst. of Washington. Publication* No. 279.

Jones, M., and Mellersh, V. (1946a). *Psychosomat. Med.*, **8**, 180.

——(1946b). *Ibid.*, **8**, 192.

——, and Scarisbrick, R. (1946). *Ibid.*, **8**, 188.

——, and Tanner, J. M. (1948). *J. Neurol., Neurosurg. Psychiat.*, **11**, 53.

Seltzer, C. C. (1940). *Amer. J. Physiol.*, **129**, 1.

Sheldon, W. H. (1940). "The Varieties of Human Physique." New York.

——(1942). "The Varieties of Temperament." New York.

Tanner, J. M. (1947). *Proc. roy. Soc. Med.*, **40**, 301.

——(1948a). (To be published.)

——(1948b). (To be published.)

——(1948c). (To be published.)

BOOK REVIEWS

DISEASES OF THE NERVOUS SYSTEM

W. Russell Brain

(London. Oxford University Press. 1947. Third edition. Pp. 937; 79 illustrations. 37s. 6d.)

This is the most comprehensive textbook of neurology in current publication from the pen of an English author, and it has already proved its value to the student and practitioner. Many additions have been made in this new edition, particularly with regard to nutritional disorders, the use of penicillin, prolapsed intervertebral disc, nerve injuries, and traumatic paraplegia.

It is disappointing to find little reference to recent advances in neuro-anatomy and physiology which add much to the students' interest in current neurological topics. It may also be suggested that the sections on shoulder girdle neuritis and Bornholm's disease are inadequate to the practitioner seeking advice on these conditions. The method given for treatment of status epilepticus does not stop the convulsions in many cases, and the urgent need to control the fits quickly is not sufficiently stressed. However, the student and practitioner will generally find all the information he requires in this book.

One cannot but admire the patient collection of facts gathered in a textbook of this kind, and yet it seems regrettable that the author does not make more effort to inspire his readers with the enthusiastic interest in neurology which the author himself possesses.

LA LIPOMATOSE CIRCONSCRITE MULTIPLE

Knud H. Krabbe and Erik D. Bartels

(Copenhagen. Einar Munksgaard. Pp. 123. No price given.)

Multiple circumscribed lipomatosis is a disorder characterized by the presence of small lipomata on the forearms, on the arms and thighs, and occasionally on the abdomen. Each tumour is smaller than a walnut, rounded, somewhat flattened; it consists of fat, and is divided by septa of connective tissue, which may cause lobulation; the tumours may be oblong, with the long axis in the long axis of the limb. The authors reckon that the disorder occurs in 5 per 1,000 of the population; in their 42 patients 37 were male and 5 female; whereas single lipomata occur more commonly in females. The tumours were found on routine examination, and were symptomless.

A curious feature of the disorder is that it progresses only for a certain time—usually about 2 years—and then becomes stationary; in some cases the tumours have retrogressed and they have been known to disappear. They come on typically between the ages of 35 and 45. The disorder is distinguished clinically from multiple neurofibromatosis by the lack of multiple cutaneous papules, café-au-lait plaques, and telangiectases, which, according to the authors, are rarely absent from neurofibromatosis; also the tumours of multiple neurofibromatosis are firmer and more firmly attached to the skin.

A knowledge of the disease, clearly important to the neurologist, is provided at perhaps unnecessary length in this work.

PHYSICAL TREATMENT OF INJURIES OF THE BRAIN AND ALLIED NERVOUS DISORDERS

K. M. Hern

(London. Bailliere, Tindall and Cox. Pp. 96+vii; 34 illustrations. 10s. 6d. net.)

Graduated physical training is perhaps the most important aspect of treatment during convalescence after head injury, whether or not there is any resulting paralysis. Miss Hern's success in handling these cases is well known to many British neurologists, and her book will be welcomed by those who realize the importance of physical re-education both after closed head injury and after brain injury causing hemiplegia or other motor disorder. The book is clearly written and well illustrated, and there is a foreword by Sir Charles Symonds.

CHILD PSYCHOLOGY

Arthur T. Jersild

(London, New York, and Toronto. Staples Press Ltd. 1947. Pp. 623+xii. Price 30s.)

This is a good textbook on the normal psychology of children. The subject is developed from the beginnings of behaviour through motor development, social behaviour, feeling and emotion, language development, the growth of understanding, make-believe and imaginative activities, ideas on morals and religion, children's interests, the growth and prediction of intelligence, to personality and the problems of adjustment. A considerable amount of factual material, provided in the form of tables, is discussed in an interesting and balanced way. Recent research is adequately covered.

PRIMARY SENSORY NEUROPATHY WITH MUSCULAR CHANGES ASSOCIATED WITH CARCINOMA

BY

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(RECEIVED DECEMBER 12, 1947)

Among the many clinical forms of polyneuritis, one that affects sensory function alone is sufficiently unusual to attract more than passing attention. In milder forms of infective polyneuritis and in unusual post-diphtheritic cases the clinical phenomena may be predominantly sensory, but evidence of muscular weakness and wasting, particularly in proximal muscle groups, can usually be demonstrated. The so-called diabetic ataxia and alcoholic tabes are also not clear-cut sensory disorders. Herpetic zona is not only confined to a single or related group of nerve roots, but is also regularly accompanied by a motor component, an anterior poliomyelitis, which is more evident if the involved segments supply the musculature of a limb. The syndrome presented below could be classed among the ataxias, presenting as it does a severe disorganization of movement. From the first the severity of loss of general sensation, beginning at the periphery of the limbs, advancing to include the trunk, and in one case the face, differentiated the clinical picture from that of tabes dorsalis. The coexistence of " myositis " was not suspected during life.

Both patients* were observed in 1939, and though the pathological material has been preserved, the part of the clinical record of Case 2 dealing with the last two months of the patient's illness was lost during the war years by the hospital where he was admitted. Sufficient, however, remains from my personal record of the earlier part of his illness to indicate the identity of the process in the two patients.

Case Histories

Case 1.—The first patient was demonstrated at a clinical meeting of the Royal Society of Medicine on Feb. 16, 1939, by Dr. D. Kendall, and the pathological material from this case was presented by the present author at a pathological meeting of the Society on May 18 of the same year.

A boiler cleaner aged 59 years was seen by me at St. Bartholomew's Hospital, London, in December, 1938, suffering from numbness of both feet, both hands, and the face. In his previous medical history the only illness of note was of a carbuncle on the neck eight years earlier. He had occasionally drunk beer, never spirits. He had not been exposed to lead or to any noxious fumes. Since about August, 1938, he had felt generally depressed but not definitely unwell. In early October, 1938, he developed an ache in his right ear radiating into the right side of the neck. After fourteen days he noticed a numbness of the soles of both feet which advanced up the legs a little in the following three days. At this time he first noticed a numbness round his mouth and this gradually spread to involve the whole face in the course of a few days. At the same time the hands were becoming numb. The numbness of face, hands, and legs thus rapidly developed in seven to ten days, then remaining fairly stationary. Throughout late December and all January he received thiamine by intramuscular injection. In early January he began to have intermittent tingling sensations in both hands and both feet. In this period he had intermittent stabs of pain in the inner aspect of the ankles and radiating to the knees and buttocks, and the numbness spread up the legs to the knees and up the forearms to above the elbows. On Jan. 20, 1939, he was transferred to the National Hospital, Queen Square, under the care of Dr. Gordon Holmes. He had no headaches, no disturbance of vision, no tinnitus or vertigo, and no dysphagia or dysarthria. There was no disorder of sphincter control. His appetite had been poor for the duration of his illness, but there was no deficiency in diet. He had lost about 30 lb. in weight in the previous six months. His stools had been natural and never tarry.

On admission to the National Hospital he was pale and thin but cheerful and co-operative in examination. Vision was unaffected and the optic discs of good colour. Ocular movements were unaffected, and no pupillary

* The two cases presented here are included with one other in a paper by R. Wyburn-Mason on " Bronchial Carcinoma presenting as Polyneuritis," in the *Lancet* of Feb. 7, 1948, p. 203, which has appeared since the present paper went to press. The detailed pathological analysis reported here does not support the theory of " reflex " production of peripheral neuritic symptoms (in analogy with pulmonary osteo-arthropathy) proposed by Wyburn-Mason.

abnormality was found. There was no nystagmus. Sensation of pain was absent over the whole face and tongue, and the corneal reflexes were absent. Sensation to light touch was also absent over the whole face, and only impaired deep sensibility and temperature sense remained. The masseters and temporal muscles contracted well, as did all the facial, palatal, and lingual muscles. There was no visible muscular atrophy. The patient was, however, quite unaware of the position of his tongue. Hearing was reduced to two inches in the right ear and two feet in the left (tuning fork) with negative Rinne in the right side. The sternomastoids and trapezius contracted well.

In the upper limbs there was no loss of power of muscular contraction, and though there was a general thinness there was no atrophy. There was severe ataxia in the finger-nose test, but posture was well maintained. The limbs felt hypotonic on manipulation. He was unable to sit up without assistance, but all trunk muscles could contract. In the lower limbs there was some reduction of power of all movements of hip and knee joints, though power of movement of feet and toes appeared natural. All muscles were small, but atrophy, greater than was accountable by general cachexia, was thought to be present in all the thigh muscles of both sides. The heel-shin test revealed gross, irregular ataxia in both lower limbs. The electrical reactions of the muscles were not ascertained.

The biceps, triceps, and supinator jerks were all present on both sides but were sluggish and difficult to elicit. The knee jerks and ankle jerks were absent in both lower limbs. No abdominal reflexes were obtained. The plantar responses were both flexor.

Sensation to pain was generally impaired over the whole body. In a few patches, on the thighs and over the abdomen, a pin prick was recognized as such, whereas in the periphery of the limbs no pain sensation remained. Sensation to light touch and to temperature was grossly defective all over. Sense of passive movement was absent at all joints. Sense of vibration remained only on the clavicles, sternum, and upper dorsal spines.

Walking was possible only with assistance, and was shuffling and grossly ataxic.

On general physical examination some clubbing of the fingers was noted but no gross respiratory signs. The heart was normal, and peripheral circulation good. Blood pressure was 120/90 mm. Hg. The liver edge was just palpable below the costal margin. No evidence of glossitis, or skin lesion was present. A search for evidence of malignant disease at that time was without result.

The cerebrospinal fluid was clear and colourless, with 1 cell per c.mm., the total protein 100 mg., the globulin (Pandy) positive, the colloidal gold 0001221000, and the Wassermann test negative. Examination of the blood showed 4,840,000 erythrocytes per c.mm., hæmoglobin 92 per cent., white cells 5,600. On Feb. 17, 1939, a trace of lead was reported in the urine but it was decided that the amount was not significant. A differential blood count was reported as follows: leucocytes 13,400 per c.mm., polymorphs 84·5 per cent., lymphocytes 14·5 per cent., eosinophils 1·0 per cent.

Soon after the clinical state reported above, on Jan. 21, 1939, the patient developed retention of urine for three days, following which he again voided naturally. Following further intensive vitamin B_1 therapy there appeared to be slight improvement in sensibility to pin prick over the upper arms and thigh by Feb. 2. On Feb. 18 he developed respiratory embarrassment and was found to have impaired breathing at the base of both lungs with a loud pleural friction at the right apex. He then developed signs of extensive pulmonary consolidation and died on March 5, 1939.

ANATOMICAL FINDINGS.—The anatomical findings were of (1) bronchial carcinoma; (2) secondary carcinomatous metastasis to stomach; (3) mild hepatitis; (4) terminal bronchopneumonia; (5) severe degeneration of the cranial and spinal dorsal root ganglia; and (6) mild chronic polymyositis.

At post-mortem examination the following abnormalities were noted. Though the brain and spinal cord appeared normal, the sensory roots of the trigeminal nerves were greyer than the motor roots, and the spinal dorsal roots were everywhere rather more grey than the ventral roots, especially in the lumbo-sacral enlargement, where they were also congested. The ganglia on these roots appeared natural but congested.

CHEST.—There was some turbid yellowish pleural fluid on the left side, and a mass of degenerating tumour was present, coming to the surface over the outer aspect of the lower lobe and connected with a firmer mass arising in the wall of the bronchus to the lower lobe. A mass of glands was present at the hilum. Some small patches of bronchopneumonic consolidation were present on the surface of the left lower lobe. The right lung was unaffected.

HEART AND AORTA.—These were healthy.

LIVER.—The liver was shrunken and rounded, and weighed 1,700 g. The cut surface was firm and rather yellow.

SPLEEN.—The spleen was rather large and soft, with some softened tumour tissue on its inner surface (from the wall of the stomach).

STOMACH.—On the upper margin, near the cardiac end but not communicating with it, was a cancerous ulceration covered on its inner surface by blackened blood. The lower few centimetres of the œsophagus were diffusely swollen, but not ulcerated. The stomach itself was much distended, but the pyloric end was normal, as were also the intestines.

KIDNEYS, SUPRARENALS, BLADDER, AND PROSTATE.—These were healthy.

MICROSCOPIC EXAMINATION.—Sections of the lung, stomach, and liver, of various levels of the spinal cord, brain stem, and cerebellum, of the right sixth and seventh cervical, first and tenth dorsal, third and fourth lumbar, and first and second sacral dorsal root ganglia and both gasserian ganglia, of the sciatic, posterior tibial, and sural cutaneous nerves, and of the soleus and gastrocnemius muscles were made and stained by a variety of methods. The tumour of the stomach and lung consisted of a solid mass of very elongated darkly stained nuclei

with no visible cell body except in mitotic cells. These were intersected but not broken up into alveoli by fine connective-tissue channels (Figs. 18 and 19). The cells were more elongated and less degenerated than in most bronchial carcinomas, and the connective tissue was less in evidence.

The liver showed some thickening of the connective tissue of the portal tracts, which in a few places completely enclosed small lobules. There was, however, very little degeneration of liver cells and no definite cirrhosis.

In the central nervous system the only abnormality was a very severe degeneration of the dorsal columns of the spinal cord (Fig. 3). Both the columns of Goll and of Burdach showed few remaining fibres throughout their length. There was no inflammatory reaction, and the degeneration was consistent with simple Wallerian degeneration of the central processes of the dorsal nerve roots. Occasional anterior horn cells, three or four in all, showed slight axonal reaction, but the remainder were of normal appearance. No abnormal granules were present in either Nissl or hæmatoxylin preparations. The brain stem and the cerebellar cortex showed no abnormality. The purkinje cells were unaltered. There was no change in the meninges of brain stem or spinal cord.

The dorsal nerve roots were severely degenerated. Those in the lumbo-sacral region showed only occasional myelinated fibres (Fig. 11) and, in sections stained by the Bielschowsky method, an occasional axis cylinder. In place of the absent fibres there was only the bands of Büngner with chains of Schwann nuclei characteristic of degenerated nerve. An occasional lymphocyte or fatty macrophage remained. The meningeal covering of the roots was of natural appearance. The ventral nerve roots were of natural appearance, without degeneration of fibres. Sections stained by the Weigert method, however, revealed a conspicuous widening of the nodes of Ranvier on every ventral root fibre (Fig. 10), and some were beaded for a segment between normal segments, but there were no fat droplets or cellular change. All the axis cylinders were uneven in calibre, presenting regular nodular swellings which appeared to correspond with the nodal loss of myelin of Weigert preparations.

The dorsal root ganglia were profoundly altered. In the lumbo-sacral ganglia hardly a single dorsal root cell remained (Figs. 1 and 2). In place of the missing cells small nests of darkly stained oval nuclei clustered within a capsule of pale oval connective-tissue cells (Fig. 6) were seen scattered uniformly throughout the ganglia. The outer capsule of these " residual nodules " (Nageotte) were sometimes laminated in several layers of connective-tissue cells (Fig. 6) but this was rare. The central cluster of true capsular nuclei were often in the form of a star, but sometimes more loosely arranged. A small darker rounded nucleus was rarely included. The connective-tissue stroma of the ganglia was slightly more cellular than normal. The blood vessels were of natural appearance except that the media of some of the arterioles showed some hyalin thickening. In one or two places a few lymphocytes surrounded a small venule. Lymphocytes and occasional plasma cells lay scattered through the tissue surrounding residual nodules (Figs. 2 and 6). Except for two isolated instances no pigment remained in the capsules, but in places fine granules of pigment remained in the fixed connective-tissue cells of the stroma. An occasional nerve fibre, intact in both myelin and axis cylinder stains, could be found in relation to an isolated surviving dorsal root ganglion cell. Few of such isolated nerve cells were of natural appearance. The remainder exhibited chromatolysis, swelling, and the nuclear change of cell disease (Fig. 9). The outer fibrous capsule of the ganglia was unaltered.

The cervical dorsal root ganglia were of the same appearance except that more surviving ganglion cells were found, (from two to ten in each section). Nearly all surviving cells showed the alterations described in the lumbo-sacral ganglia. The gasserian ganglion presented the same disappearance of ganglion cells, complete in the lateral two-thirds of the ganglion (Fig. 5). In the inner third many ganglion cells remained. Here, and occasionally in the cervical ganglia, some remaining nerve cells exhibited partial damage with loss of chromatin, ragged outline, and subcapsular proliferation of dendrites. Where such proliferation was occurring there was also swelling of the capsular cells, and proliferation of the outer capsule. The appearance of a laminated outer capsule in some " residual nodules " would correspond to the death of the cell body after an earlier stage of subcapsular and capsular proliferation.

The loss of all the dorsal root fibres was in striking contrast to the compact undegenerated ventral root as it passed the ganglion, and as it merged into the peripheral spinal root (Fig. 1). As the motor fibres became spread out in the combined spinal root some irregularity of calibre was clear. Each fibre attenuated to a thin thread at the node of Ranvier (Fig. 12), and was thickened, often tortuous, in the internodal segment. The greatest thickening, sometimes an actual swelling, occurred at the Schwann nucleus in the mid-internodal region. Nevertheless, there was no fragmentation of axis cylinders or myelin in motor fibres. In one place, in one section, ventral to the first sacral ganglion, a few fibres of the ventral root were all greatly swollen as they passed a small venule near the perineurium. There was no cellular change or other evidence of inflammation. The vessels of the nerve appeared normal.

The grey ramus communicans was clearly seen and was full of non-medullated fibres (Fig. 12). Though no sympathetic ganglia were sectioned there was this evidence that sympathetic cells were not destroyed.

The peripheral nerves showed varying mixtures of intact nerve fibres of even calibre, presumably nearly all motor, and degenerated bands of Büngner (Figs. 4 and 8). A few residual globules in phagocytic cells stained with Weigert's method, but otherwise most fat globules, phagocytes, and other evidence of degeneration had disappeared, leaving only quiescent Schwann bands. The remaining axis cylinders showed the same irregularity of calibre which was evident in the motor nerve roots. In a sensory nerve (Fig. 7) no intact myelin sheaths remained. The nerves entering the muscles showed the loss of one-third to one-half of the fibres.

The muscles were pale and thin. On section there was a considerable increase in cellularity (Fig. 13). The nuclear increase was chiefly due to the large number of muscle nuclei. The rod-shaped nuclei immediately under the sarcolemma were increased in number in every fibre, and in many there were in addition oval pale nuclei embedded in the striate substance. In some large fibres the centrally placed nuclei were arranged in long columns, and in this case they tended to a narrow, blunt-ended, shape, as if compressed. The endomysium was more than twice as cellular as normal, the increase being due to the presence of many histiocytes and occasional small lymphocytes. The histiocyte nuclei stained darkly with hæmatoxylin, with poorly developed nucleoli (seen between the muscle fibres in Figs. 13, 16, and 17). There was no change in the blood vessels, and no lymphocytic or other infiltration. The muscle fibres varied greatly in diameter, some being more than twice natural size, most being thin, and a few reduced to chains of nuclei within a membrane. This variation was irregular and haphazard. Swollen fibres had diminution or absence of cross striation and stained poorly with hæmatoxylin. Longitudinal striation was more prominent in such fibres. No vacuolation of the muscle fibres was seen. In places isolated large muscle fibres showed clumping of the sarcoplasm of one segment of the contents, but there was rarely any cellular reaction to such a mass. In the few exceptions the muscle nuclei had clumped on either side of the coagulated segment, as if the process had been very recent. No isolated hyalin masses or multinucleated aggregation were found.

With the Bielschowsky method good impregnation of large numbers of nerve endings in muscle was obtained. The intramuscular nerve plexuses were of normal appearance, and it was clear that degeneration of motor fibres had not occurred. There were many normal motor endings on normal muscle fibres, and these accounted for approximately fifty per cent. of the motor endings seen. Other axis cylinders showed, however, the same irregularity in calibre as in their more proximal course, except that the swellings were here more isolated beads, the remainder of the axis cylinder greatly attenuated. As the nerve fibre reached the motor ending of a swollen, altered, muscle fibre it became very thin, and the terminal ramification in the end plate was swollen, resembling a leaf on a thin stem (Figs. 14, 15, and 17). The nuclei of the end plate were clumped peripherally in a semicircle, but otherwise of natural appearance. This curious reversal of the relative size of nerve fibre and terminal ramification was most clear on large swollen muscle fibres. Very thin atrophic fibres showed only one or two slender axis cylinder branchings within the end plate, each ending in a leaf-shaped bulb. Just before the axis cylinder reached the end plate in such fibres a thickening was present and in a few a budding proliferation had occurred at this point (Figs. 14 and 15). On some large muscle fibres which still showed striation but having swollen and unusually obvious sarcolemmal nuclei the motor ending was greatly swollen (Fig. 16). This was interpreted as the first change in response to the process of hyalinization of muscle. Two muscle spindles were studied. Each lacked a sensory ending, but retained motor endings with beaded processes. The intrafusal muscle fibres were unchanged.

The sympathetic nerve fibres accompanying the blood vessels in muscles were present, unchanged.

Case 2.—A retired Army Colonel, aged 71 years, was first seen by us on Oct. 1, 1939, when he complained of unsteadiness in walking for three months. His consumption of alcohol had been high in middle life but had greatly lessened in the ten years preceding his illness. There was no history of neuritic illness prior to the present complaint. He had suffered from mild osteo-arthritis in the left knee for three years. In February, 1939, he had an attack of influenza, and though this was considered mild he had never felt well since. Early in July he found that both legs were unsteady in walking, and about the same time noticed a feeling of pins and needles in the fingers and toes. Gradually in the next three months the paræsthesiæ in the extremities gave place to numb, dead feeling, movement of his legs became very uncertain, and his hands clumsy and awkward. He frequently fell if he attempted to walk without support. There was no affection of vision, of speech or of swallowing, and no disturbance of micturition. On examination on Oct. 1 he was found to be grossly ataxic in gait, and quite unable to walk alone. There was no disorder of the cranial nerves except for some slight slurring dysarthria in speech. There was no glossitis. In particular the pupils were of moderate size, equal, and reacted briskly to light and accommodation. There was no disturbance of facial sensation.

The power of movement in both upper and both lower limbs was excellent but unsteadily maintained. There was extreme inco-ordination, so that in the finger-nose test the finger would strike parts of the face or neck, and in the heel-knee test he was unable to complete the movement owing to gross unsteadiness. The bulk of all muscle groups was thin, but there was no focal wasting, and no notable weakness of any single muscle. He was unable to keep still except in complete relaxation, which he had great difficulty in reaching.

No tendon reflexes were obtainable in biceps, triceps, supinator, quadriceps, or sural triceps. The abdominal reflexes were absent, the plantar responses both flexor.

Sensation to pin prick was diminished over the upper limbs peripheral to the elbows, and over the lower limbs below the midthigh. There was some slight hypalgesia as high as the level of the umbilicus. Over both forearms, and below the knees, there was no remaining pain sensation. Sensation to touch was greatly diminished below the elbows and below the knees. Sense of vibration was very poor but present at the knees, and felt faintly in the ankles. Position sense in the hands and feet was entirely absent.

He was admitted to the National Hospital, Queen Square, and remained there until his death on Feb. 5, 1940. It is known that his blood Wassermann was negative. The blood count on Nov. 14, showed 3,500,000 red blood cells per c.mm., Hb 70 per cent., colour index 1·0, 11,600 white blood cells per c.mm., polymorphonuclears 73 per cent., lymphocytes 25 per cent.,

eosinophils 2 per cent. On Dec. 13, 1939, the blood count was 4,160,000 red blood cells per c.mm., Hb 66 per cent., colour index 0·8, leucocytes 25,200 per c.mm., polymorphs 85 per cent., lymphocytes 13 per cent., eosinophils 2 per cent. The case record has unhappily been lost during the war years. Though he had not complained of any respiratory disorder, he was found on admission to be suffering from a persistent cough with tenacious sputum which he stated he had had for some weeks. At this time the physical signs in the chest were those of chronic bronchitis. In the next month he became more ataxic, and pain sensation was entirely lost over all four limbs, and greatly diminished over the trunk up to a vague transition over the lower costal cartilages. Sense of touch, temperature, and vibration were also gradually lost over all four limbs. Muscular power remained full, and though he was generally thin none of the muscles was truly atrophic. Two episodes of pneumonitis, with fever and consolidation at both bases were survived in the following three months, but he developed bed sores and succumbed to terminal pneumonia on Feb. 5, 1940.

ANATOMICAL FINDINGS.—These were: (1) bronchial carcinoma; (2) megacolon and dilated stomach; (3) severe degeneration of the spinal dorsal root ganglia; and (4) severe polymyositis.

The findings at the post-mortem examination were as follows:

CHEST.—The right lung was very adherent to the chest wall. Its substance was throughout firmer than normal, with much œdema and slight consolidation, and at its root was a large mass of carcinoma attached to a mass of greatly enlarged adherent glands in the anterior mediastinum. A small abscess with necrotic centre and very friable walls was present in the centre of the lower lobe. The left lung was healthy.

HEART AND AORTA.—These were healthy except for some atheroma, especially in the abdominal portion.

LIVER.—The liver was normal, but displaced to the right by great enlargement of the colon and dilatation of the stomach.

SPLEEN.—The spleen was rather large and firm.

STOMACH.—The wall was of normal thickness, the mucosa atrophic, and the organ unduly large, but not to such a degree as the colon. Small intestine of usual size. The colon was enormous throughout, about 4 inches in diameter. Even the rectum was considerably larger than normal.

KIDNEYS AND SUPRARENALS.—These organs appeared to be healthy.

MICROSCOPIC EXAMINATION.—Pieces of lung, stomach, liver, kidney, spinal cord, nerve roots, sciatic, anterior and posterior tibial nerves, median and internal cutaneous nerves, gastrocnemius and soleus muscles were stained by a variety of methods. Histologically the tumour in the lungs was composed of small oval cells with darkly-stained nucleus and fairly well-defined small cell body (Fig. 30). Mitoses were numerous. These cells lay in irregularly shaped masses separated by thin strands of collagen, and where the cells lay against these collagen fibres some were arranged in palisades and appeared almost columnar. In other places small rings of tumour cells were seen suggesting an attempt at acinar formation, but for the most part the cells were scattered quite irregularly. The tumour was considered by Dr. J. G. Greenfield to be an "oat-celled" bronchial carcinoma.

No abnormality was noted in the liver, stomach, or kidney.

Sections of the spinal cord at various levels showed a severe degeneration of the dorsal columns (Fig. 24), secondary to degeneration of the dorsal nerve roots, in myelin sheath stains. No disorder was found in the anterior or lateral columns, and the anterior nerve roots were of normal appearance in cross section. One or two anterior horn cells in each section showed a mild axonal type of reaction in the form of powdering of the cytoplasm and peripheral displacement of the nucleus. Such axonal changes were minimal in degree and were most evident in the lumbo-sacral region. The remaining anterior horn cells were of normal appearance. No abnormal granules were seen. There was no inflammatory reaction of the meninges, and glial changes were limited to a mild chronic change accompanying the secondary degeneration in the dorsal columns.

The dorsal nerve roots were severely degenerated (Fig. 23) with occasional persistent phagocytes containing products of myelin degeneration. Here and there a more recently degenerate fibre was represented by a line of vacuolated phagocytes with fragments of myelin. The surviving fibres showed widened nodes of Ranvier. Many finely myelinated fibres were present (Fig. 23). In axis cylinder stains these had the finely beaded appearance of regenerated fibres and could be traced back into the corresponding ganglia.

The ventral nerve roots showed no loss of fibre content, but in myelin stains the myelin sheaths were irregular, with gaps at the nodes of Ranvier in a few fibres, and vacuolation of the myelin at this point in many fibres. In axis cylinder stains considerable irregularity of calibre was noted, but not as extensive as in Case 1.

The dorsal root ganglia showed loss of approximately 50 per cent. of nerve cells in the lumbo-sacral region, and of 30 per cent. in the first thoracic ganglion. Residual nodules, identical with those seen in Case 1, replaced the missing cells (Fig. 20). The remaining cells were in general pale and swollen, and nearly all showed intracapsular and subcapsular proliferation of dendrites (Fig. 21). One or two ganglion cells in each section were shrunken, darkly stained, and atrophic, with proliferation and swelling of the nuclei of the subcapsular cells. One such appears on the lower right side of Fig. 20. The remaining nerve fibres in the ganglion were swollen and stained darkly with axis cylinder stains, except for some finely beaded accompanying plexuses (Fig. 21). The connective-tissue stroma of the ganglia, and the vessels traversing it, were of natural appearance. A few scattered lymphocytes were seen in the connective tissue, and in three places small perivascular accumulations of lymphocytes had occurred. The outer capsules of the ganglia and periganglionic tissues were unchanged.

The first thoracic dorsal root ganglion presented numerous examples of agonal proliferation of dendrites,

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with protrusions from the cell body in later stages (Fig. 22). The final stages were represented by shrinkage of the cell body until only a stump of argentophil substance remained among the swollen capsule cells. With disappearance of such stumps the pericapsular plexus also disappeared, leaving the "residual nodule" of capsular cells.

Each ventral nerve root, where it passed the corresponding dorsal root ganglion, was robust and presented only mild irregularity of myelin sheath and axis cylinders. In the sciatic nerve there was loss of between one-half and one-third of the fibres in each bundle, and some occasional myelin debris remained. There was no inflammatory reaction or œdema of the perineurial spaces. The same changes were found in the posterior tibial (Fig. 25) and median nerves. The residual fibres often showed gaps at the nodes of Ranvier.

The muscles showed a considerable amount of proliferation of connective tissue and sarcolemmal nuclei with swelling of isolated fibres. This change was more advanced and generalized than in Case 1 (Figs. 26 and 28), and had excited a moderate histiocytic reaction.

In most areas of gastrocnemius or soleus muscles less than 20 per cent. of muscle fibres retained both cross striation and relatively normal diameter; even in these there was an increase of sarcolemmal nuclei, often in long rows. The remaining muscle fibres were mostly pale staining and swollen to twice the normal diameter, with great increase in numbers of nuclei. About ten per cent. of fibres were reduced to small chains of pyknotic nuclei with no recognizable striate or sarcoplasmic substance, as in the upper part of Fig. 28. The largest fibres in one portion of gastrocnemius appeared to have broken into discontinuous hyaline and often vacuolated masses which stained irregularly with silver (Fig. 29) and not at all with hæmatoxylin or thionin (Fig. 27). Such masses contained two types of rounded nuclei, about half of which were pyknotic, the others pale and swollen (Fig. 27). Rarely a polymorphonuclear leucocyte was seen in the centre of such a hyaline mass. At an intermediate stage of hypertrophy of muscle fibre the whole fibre exhibited metachromatic staining with thionin (as do two fibres in the lower half of Fig. 27), but otherwise the larger the fibre the less deeply it stained with thionin or hæmatoxylin. Some diffuse argentophil property was retained by the sarcoplasm even to the most degenerate stage (Fig. 29).

The earliest stage of the process appeared to be proliferation of the nuclei lying just under the sarcolemma, as in the large fibre in Fig. 28. Rows of sarcoplasmic nuclei then appear, and the muscle substance at this stage usually had lost the transverse striation and developed a homogeneous appearance as in the upper and lower fibres in Fig. 26. At this stage some fibres showed intermittent densification and swelling, as if tending to rupture into segments. The dense areas showed an accumulation of pale oval sarcoplasmic nuclei, the thinner areas leaving clumps of darkly stained smaller true sarcolemmal nuclei, as in the middle fibre in Fig. 26. Such segmented fibres then became separate hyaline masses as in Fig. 27. The more numerous other fibres which degenerated without segmentation passed through stages of phagocytosis and shrinkage, as in the upper part of Fig. 28, and residual clumps of pyknotic sarcolemmal nuclei, without visible membrane or cytoplasm, as seen at the bottom of Fig. 28, then remained as the last residue of the degenerated fibre. There was no calcification of the damaged segments.

There was a diffuse increase of fibroblasts throughout the endomysium, and, though wandering histiocytes, lymphocytes, and plasma cells were frequent, there were no cellular accumulations or "lymphorrhages." The blood vessels were of natural appearance. The terminal fasciculi of motor nerves as they reached the end plates showed no degeneration. A few preparations of motor nerve endings were made, and these showed thickening of the terminal arborization in the end plates of moderately swollen muscle fibres. There was only a slight increase of collagenous tissue. The tendon aponeuroses showed no change.

Discussion

The most remarkable change in the two patients presented was the severe loss of nerve cells in the dorsal root ganglia, without corresponding change in the ventral roots. No trace remained of the majority of affected cells, their empty capsules alone marking their previous situation. The small clump of satellite cells which clustered in each shrunken capsule is the "residual nodule" noted by Nageotte (1907) in his description of the process of necrosis of the nerve cells in transplanted dorsal root ganglia. Such residual nodules have been seen in the ganglia in tabes dorsalis by a number of writers (Thomas and Hauser, 1904; Marinesco and Minea, 1907; Bielschowsky, 1908; de Castro, 1932) though they were then infrequent, for the nerve cells are rarely lost in that disease. They have also been noted in severe infective neuritis of the ascending (Landry) type by Demme (1932), Juba and Szatmári (1937), Peters and Scheid (1938). According to Nageotte (1907) the "endothelial" satellite (amphicyte) cells multiply and erode the degenerated nerve cells in ganglionic grafts, but the final phagocytosis of the remnants of the cell is performed by histiocytes ("star cells" of Cajal) which penetrate the capsule and engulf the remains of the ganglion. The final stage in our cases is consistent with such a process.

In the two cases presented here a number of intermediate changes in the process of disintegration of the ganglion cells was seen. The most common in Case 1 was an acute swelling of the ganglion cell with nuclear change and chromatolysis. In Case 2 a more chronic irritative change was evidenced by swollen satellities with spiral subcapsular and capsular proliferation of dendrites. Vacuolated cells were not seen, but ragged or "erethrized" cells (de Castro, 1932) were common. The remaining cells were of both large and small types. There was no evidence of proliferation of the satellite cells,

which appeared to be swollen but in normal number. In the final stage the nuclei of the satellite cells stained darkly with hæmatoxylin or Nissl stains and became spindle shaped. Whether or not the residual nodule was surrounded by single or multiple concentric lamination of pale endoneurial fibroblastic nuclei appeared to depend on the presence or absence of proliferated capsular dendritic skeins at the time of ultimate disappearance of the nerve cell. Where such whorled dendritic nets surrounded a damaged but persistent nerve cell, the capsular proliferation of fibroblastic nuclei already existed in full development.

In this reaction the satellite cells behave in a manner comparable to the Schwann cells of peripheral nerve, at first swelling and deforming degenerating axoplasm, and later becoming spindle shaped with dark rod-like nuclei. The capsular cells have the staining characteristics of the peripheral cells that we have elsewhere (Denny-Brown, 1946) called "endoneural fibroblasts." In no instance in spinal or gasserian ganglia was any cell resembling the glia of the central nervous system observed.

The whole process of ganglionic degeneration presented the appearance of a primary atrophic process of the nerve cells, without inflammatory or vascular reaction. When nerve fibres had disappeared the parent cells had also vanished. Only in the second case was there any sign of abortive regeneration in the form of fine fibrils in the sensory nerve roots, and this was uneven and ineffective. In both instances the lumbo-sacral ganglia were the most heavily affected, but the disorder was widespread.

In contrast to the ganglionic changes in tabes the degeneration of the peripheral process of the ganglion cell was as severe as of the central. In both central and peripheral axis cylinder processes of the few surviving dorsal cells the changes were seen in irregularity of myelin and axis cylinder. A sensory neuronic degeneration was described in the neuritic ("polyradiculoganglionic") form of Landry's paralysis in examples of that disease reported by Demme (1932), Juba and Szatmári (1937), and Peters and Scheid (1938), but in that disease only a relatively small number of the ganglion cells were reduced to residual nodules. Further, the ganglia, and both motor and sensory nerve roots were the seat of intense inflammatory changes, which persisted for as long as four months (Marinesco and Draganescu, 1930). Motor paralysis was profound. Such inflammatory and motor changes were absent in the cases reported here. In even greater degree the condition differs from the necrotic lesion of herpes zoster.

From the physiological point of view the condition presented a unique example of deafferentation in man. The muscular nerves showed the large deficiency (from one-third to one-half) in nerve fibres shown to occur after excision of the dorsal root ganglia in animals (Sherrington, 1894). There was no evidence of the presence of efferent fibres, or of sympathetic collaterals in the human dorsal root or dorsal root ganglion, for the few residual fibres in these structures were fully accounted for by remaining ganglion cells. The hypothesis of Kuré and his associates (1928), that certain small axons in the dorsal roots are efferent fibres, receives no support from our material.

Though degeneration of the motor nerve roots and peripheral motor apparatus had not occurred in our cases, slight histological changes of a peculiar type were present. These changes were present throughout the length of the motor nerve fibre and consisted of a thinning of the axis cylinder and loss of myelin at the node of Ranvier, with a tortuosity and swelling in the internodal segment. There were no Erzholz granules. This type of change we have shown elsewhere to be an elementary mode of reaction related to disorder of metabolism such as ischemia, and is not necessarily associated with the impairment of conduction (Denny-Brown and Brenner, 1944). The anterior horn cells were unaffected except for occasional mild axonal reaction. No abnormal pigment was found.

The muscles also presented an unusual type of change. Proliferation of sarcolemmal nuclei and increased cellularity of the connective tissue of a kind seen in chronic myositis, or rapidly progressive myopathy were found in both cases. This change was most intense in Case 2. A portion of the gastrocnemius muscle of this case showed extensive hyaline degeneration, of Zenker type, with fragmentation of swollen muscle fibres into large ovoid masses of multinucleated sarcoplasmic material. Similar masses were scattered through the remainder of the muscle. In Case 1 some of the larger muscle fibres showed clumping of the muscle substance into segments, but the change was recent, though ante-mortem. Such fragmentation suggests the possibility of the effect of physical damage such as might occur with the stretching of swollen hyalinized muscle. Its more frequent occurrence in one part of the muscle is in favour of this view. The widespread, generalized, atrophic process, passing through stages of swelling and nuclear proliferation, which led to phagocytosis and erosion, then thinning and disappearance of the contractile substance, is considered by us to be the fundamental process. The relatively slight degree of interstitial reaction, and its complete absence in the earliest

stage (as in Case 1), indicate a primary degenerative disorder of the muscle fibre.

The signs of regeneration of muscle fibre commonly encountered in the Zenker type of degeneration of typhoid, typhus, and epidemic influenza, and consisting of multinucleated protoplasmic masses and spindles (Lorenz, 1898 ; Forbus, 1926 ; von Meyenberg, 1929) were not seen. The few multinucleated masses that were found were clusters of small very dark pyknotic nuclei without cytoplasm, lying free in the connective tissue as sole remnants of a completely destroyed fibre. Such masses appeared to be no longer viable. There was no regenerative process. The proliferative reaction of the nerve endings seen in Case 1 has been observed by us also in cases of polymyositis. The usual atrophic changes of neuritic muscular atrophy were lacking. The lymphorrhages of acute myositis were also absent, and there was a diffuse affection of muscle fibres instead of the greater degeneration at the edge of the muscular fasciculus common in that disease, which has been reviewed by Lorenz (1898), Marinesco (1910), von Meyenberg (1929), and Burton and his associates (1923). A mild eosinophilia in Case 2 recalls the similar reaction in " polymyositis."

The condition therefore, points to a diffuse degenerative process affecting primarily dorsal root ganglion cells, associated with a degeneration of striped, voluntary, muscle fibre. The slight changes in myelin and calibre of axis cylinders of motor nerve fibres was seen also in surviving dorsal root fibres. The anterior horn cells did not show any changes of the type seen in dorsal root ganglion cells. It is considered possible that the motor neurone was beginning to show a lesser degree of degenerative disorder in the form of reactive changes in the myelin. The ganglionic degeneration of the dorsal roots provides an example of a purely degenerative disease of these cells, rarely seen in man, and of special interest in contrast with the tabetic process. From the clinical point of view the progressive numbness and ataxia, without pain, reflected the ganglionic degeneration.

Degeneration of the dorsal columns of the spinal cord, of the dorsal nerve roots and peripheral nerves, but with only slight lesions of the ganglia, was found by Zimmerman and his associates (1934, 1937, 1943) as a delayed effect in experimental deficiency in thiamine, riboflavin, and nicotinic acid in animals. In these circumstances the neurites of the sensory neurone are severely affected, and the ganglion cells rarely degenerated. The only disorder comparable to the simple ganglionic degeneration seen in our two cases is the remarkable ataxia of swine studied by Wintrobe and his colleagues (1938, 1940, 1942). This disorder was produced by feeding swine a basal diet consisting of crude casein, sucrose, and lard and salt mixture, plus cod-liver oil, ascorbic acid, and yeast (1940). Many dorsal root ganglion cells disappeared, leaving only residual nodules, the remainder showing shrinkage and prominent capsular cells. Irregular swelling of myelin was found in the peripheral nerves. The dorsal columns of the spinal cord were severely degenerated and in places there was patchy vacuolar change. The lumbar ganglia were more severely affected than the cervical or thoracic. In later experiments (Wintrobe and associates, 1942) various vitamin supplements were added to the diet. The ataxia and corresponding changes in the dorsal root ganglia, dorsal roots, dorsal columns, and peripheral nerves, occurred only when the supplements did not contain either calcium pantothenate or pyridoxine. If pantothenic acid were lacking a subacute inflammation of the colon was found in addition. If pyridoxine was absent epileptiform convulsions and anæmia occurred in addition to the ataxia. Neither of these disorders was present in our cases, but our Case 2 exhibited an enormous megacolon.

Follis and Wintrobe (1945) have more recently reported that the ganglionic degeneration was found to be more prominent in further experiments on deficiency in pantothenic acid than in pyridoxine deficiency. In the latter the degeneration was thought to begin in the peripheral extremities of the nerves as much as in the ganglia. Swank and Adams (1948) found only a difference in degree of ganglionic lesion, which was greater in pantothenic acid deficiency.

We have recently reviewed (Denny-Brown, 1947) the " nutritional ataxia " encountered in prisoners of war and others after long periods of subsistence diets composed chiefly of cereals. We concluded that the ataxia in these circumstances was related to damage to the dorsal columns of the spinal cord and was not comparable to the disorder described by Wintrobe and others. The condition described here differs in many respects, notably in its neuritic symptomatology and pathology and in the absence of retrobulbar neuritis, from " nutritional ataxia." These two cases present the first clear clinical picture closely resembling experimental pantothenic acid deficiency.

The muscular changes in our cases were an unexpected finding. Wintrobe, Miller, and Lisco (1940) found " occasional hyaline and necrotic fibres " in the muscles of the thigh in five out of fourteen animals suffering from porcine ataxia. Since these investigators found similar lesions in normal animals, and in one pig fed on wheat germ oil, no conclusion was reached. On the other hand,

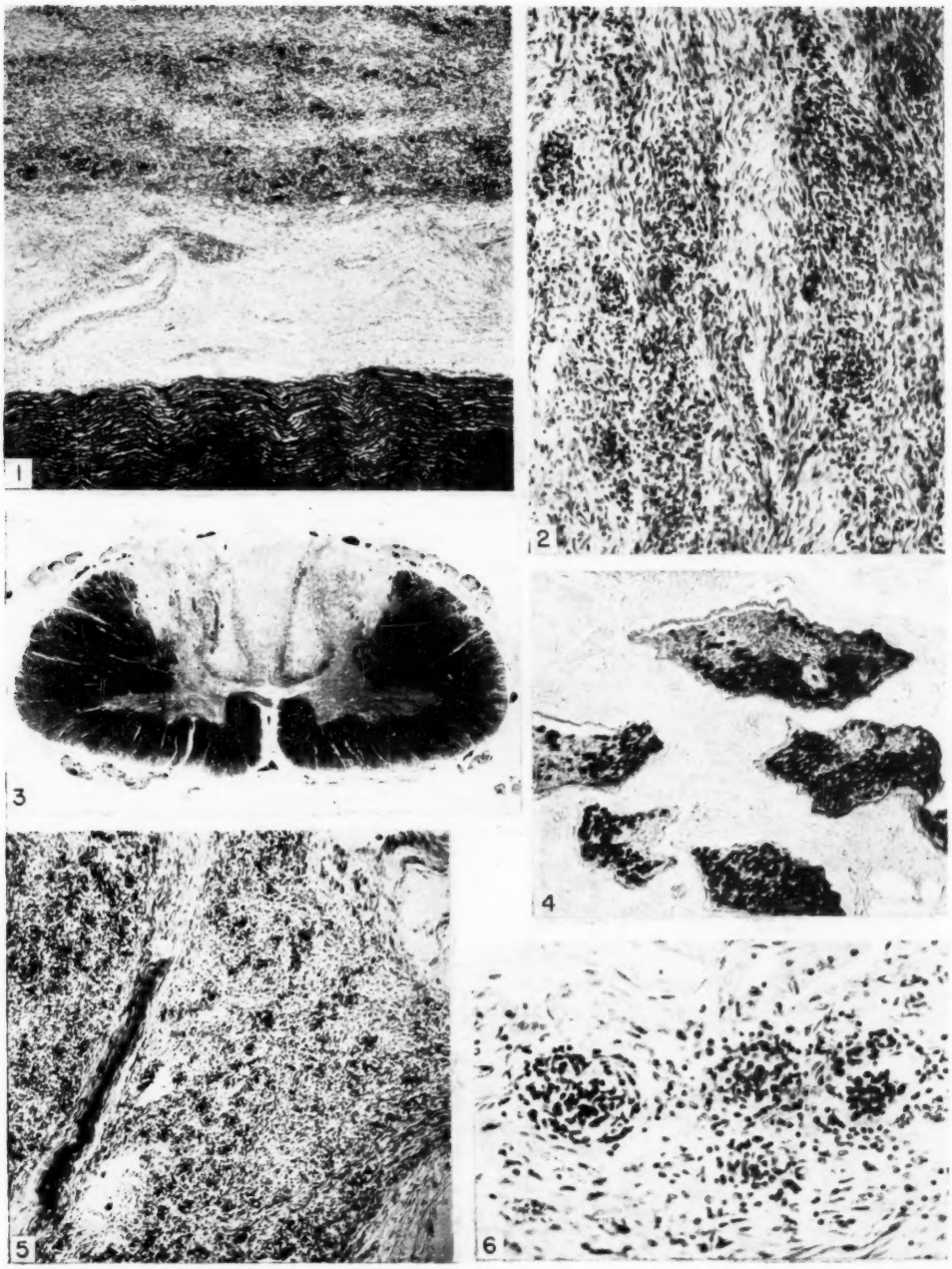


FIG. 1.—The left second sacral dorsal root ganglion of Case 1. Gros-Bielschowsky silver impregnation, counterstained with iron hæmatoxylin. The ventral border of the ganglion is shown above, devoid of nerve cells or fibres. The intact ventral nerve root passes in the lower part of the figure, separated from the ganglion by the normal fibrous capsule.

FIG. 2.—Higher magnification of the same dorsal root ganglion to show the residual nodules, empty Schwann sheaths, and connective tissue. Iron hæmatoxylin and Van Gieson.

FIG. 3.—Cervical spinal cord of Case 1. Weigert method.

FIG. 4.—Portion of left sciatic nerve of Case 1. Weigert method.

FIG. 5.—Left gasserian ganglion of Case 1. Gros-Bielschowsky and hæmatoxylin. A strand of intact sympathetic fibres passes vertically through the centre of the figure. This part of the ganglion is devoid of sensory cells or fibres.

FIG. 6.—Residual nodules, stained with hæmatoxylin and Van Gieson method.

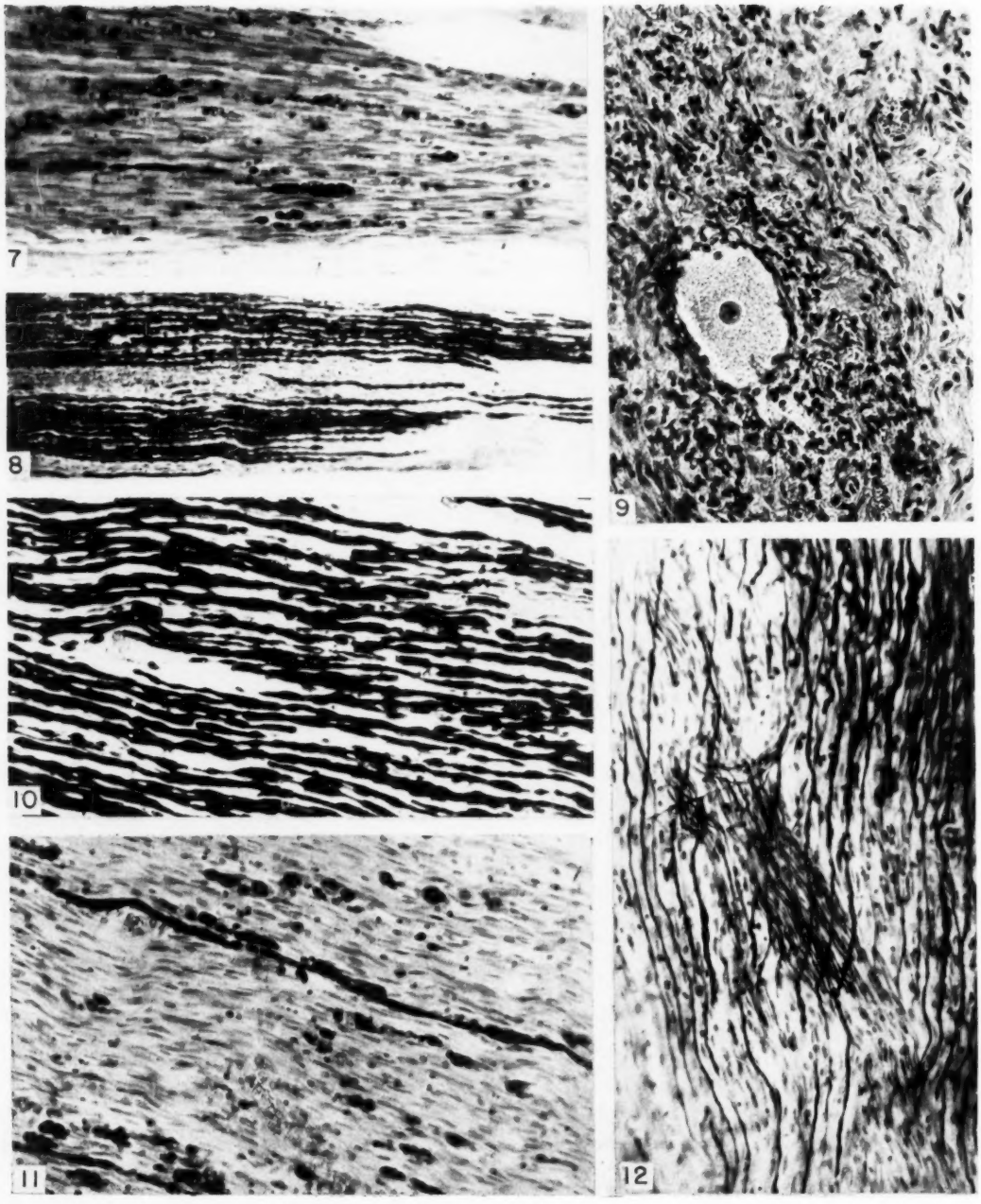
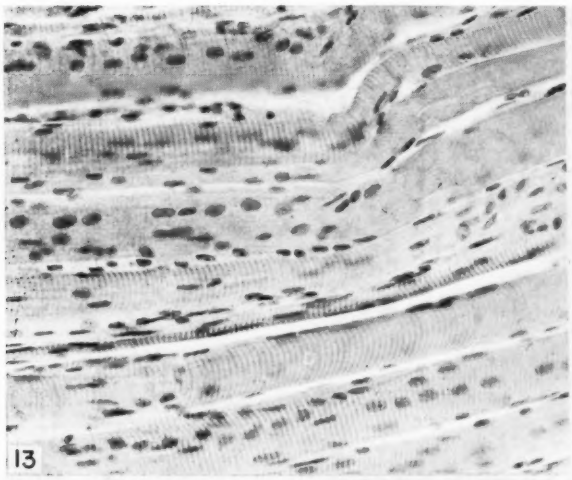
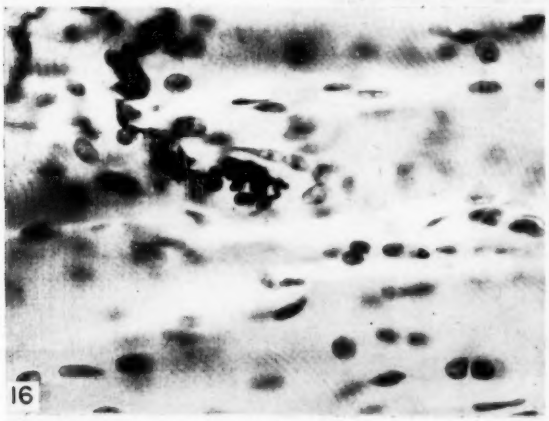
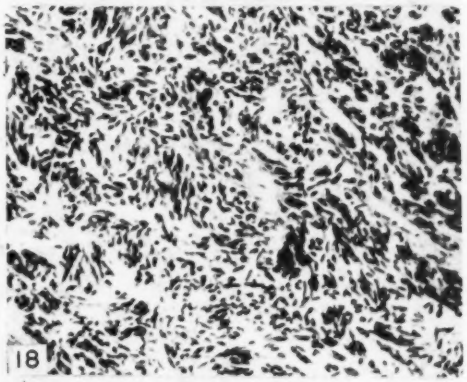


FIG. 7.—Sural cutaneous nerve. Case 1. Weigert method.
FIG. 8.—Posterior tibial nerve. Case 1. Weigert method.
FIG. 9.—A remaining dorsal root ganglion cell, first dorsal ganglion, iron hæmatoxylin and Van Gieson.
FIG. 10.—Third lumbar ventral nerve root. Case 1. Gros-Bielschowsky method.
FIG. 11.—Third lumbar dorsal nerve root. Case 1. Weigert method.
FIG. 12.—Second sacral nerve root distal to the ganglion, Case 1, to show region of junction of sensory and motor fibres with the grey ramus communicans. The intact large fibres come from the motor division. The sympathetic bundle passes obliquely across the figure. Gros-Bielschowsky method.







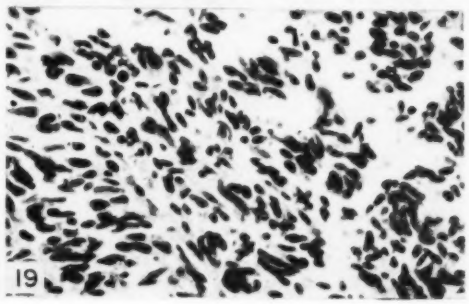


FIG. 13.—Muscle, Case 1, stained with hæmatoxylin and Van Gieson, to show the milder generalized types of change.

FIG. 14.—Motor nerve ending on a swollen hyalinized muscle fibre. Case 1. The knob just before the fibre reaches the Y-shaped terminal is a beginning of budding. Gros-Bielschowsky method.

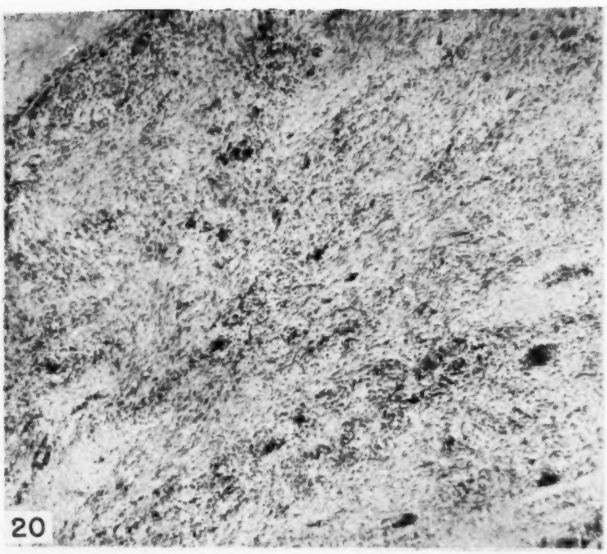
FIG. 15.—Another motor ending, low down in the right half of the figure, with sprout passing vertically up from the middle of the figure, ending in a ball.

FIG. 16.—The early swelling of the motor termination.

FIG. 17.—To show two sprouts from the end-plate of a hyalinized muscle fibre.

FIG. 18.—Case 1, section of the tumour. Hæmatoxylin and eosin.

FIG. 19.—Higher magnification of the same tumour.



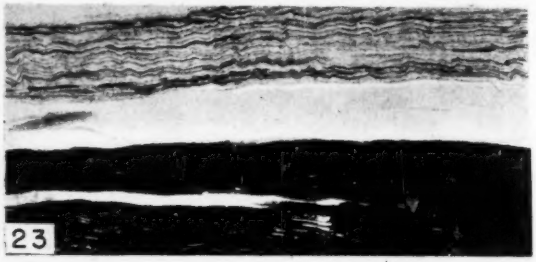


FIG. 20.—Fifth lumbar dorsal root ganglion of Case 2. Hæmatoxylin and Van Gieson. One intact ganglion cell is seen near the right border of the figure.
FIG. 21.—First thoracic dorsal root ganglion, Case 2. Gros-Bielschowsky stain. Hæmatoxylin counterstain.
FIG. 22.—Higher magnification of two residual ganglion cells and a residual nodule from the upper part of Fig. 21.
FIG. 23.—Meningeal portion of fifth lumbar nerve roots, Case 2. A dorsal rootlet lies at the top of the figure, a motor rootlet below. Weigert method.
FIG. 24.—Cervical spinal cord, Case 2. Weigert.

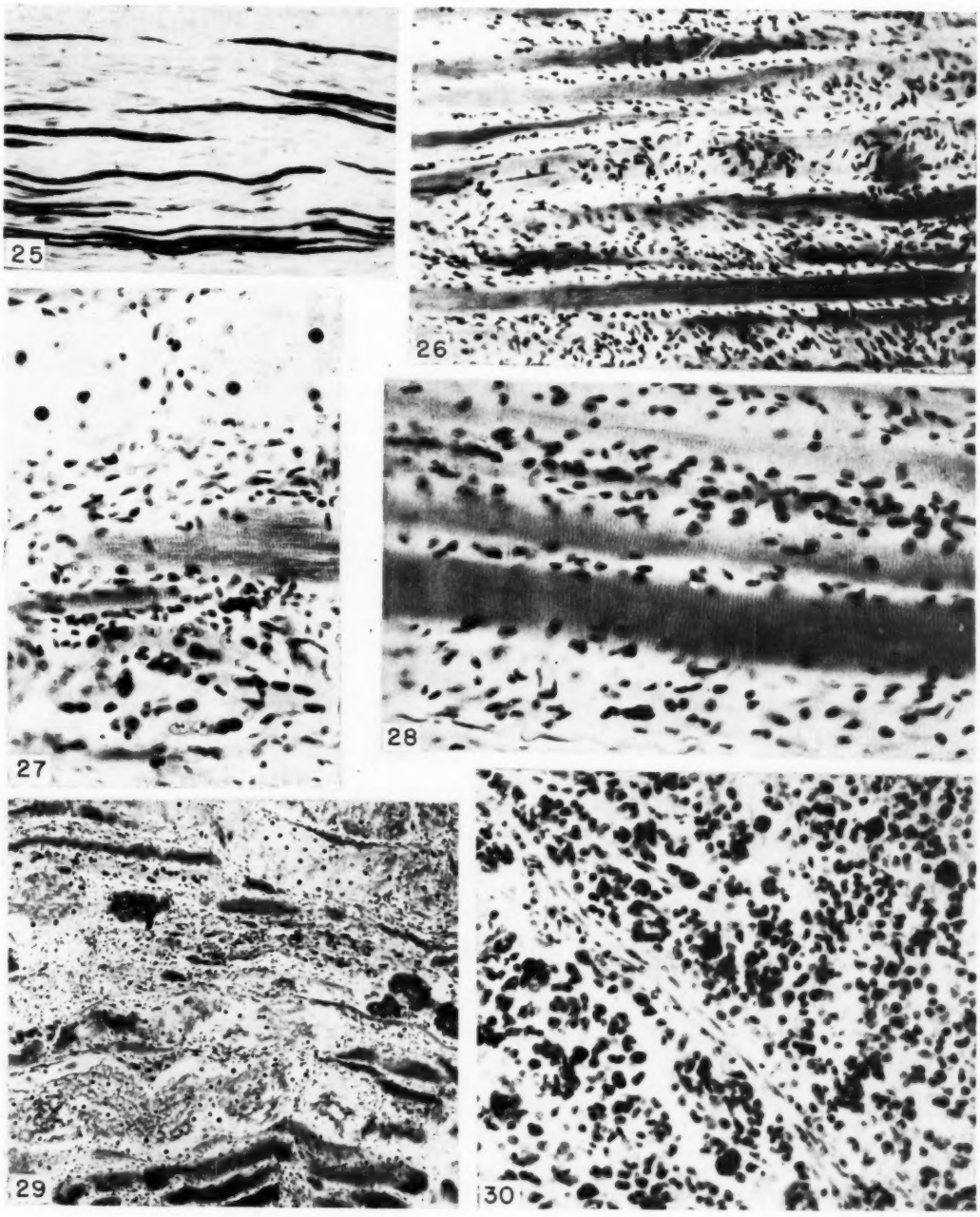


FIG. 25.—Sciatic nerve, Case 2. Gros-Bielschowsky method. Two nodal gaps are seen in the upper left corner of the figure. Corresponding Weigert preparations showed loss of myelin at the nodes.
FIGS. 26, 27, 28, and 29.—Gastrocnemius muscle, Case 2, stained by Gros-Bielschowsky method and thionin.
FIG. 30.—Section of the pulmonary carcinoma, Case 2. Hæmatoxylin and eosin.

myopathic degeneration of the hyaline or Zenker type is characteristic of the disorder produced by deficiency in vitamin E (Goettsch and Pappenheimer, 1931 ; Pappenheimer, 1939). These investigators did not find any histological change in the central nervous system. On another diet deficient in vitamin E similar myopathic degeneration was produced in ducklings (Pappenheimer and Goettsch, 1934), though the same diet induced an encephalomalacia in chicks (Pappenheimer and Goettsch, 1931). Einarson and Ringsted (1938) found that rats fed on a diet deficient in vitamin E developed degeneration of the dorsal nerve roots and dorsal columns of the spinal cord with minimal or completely absent pathology in the dorsal root ganglia. In later stages degeneration of motor nerve roots and muscles occurred. Morgulis and others (1938), noting that rats may survive and thrive for several generations on diets deficient in vitamin E which induced muscular dystrophy in rabbits, are still not absolutely convinced that vitamin E is the sole factor leading to muscular changes.

The muscular degeneration in our two patients presents the essential histological changes described in the experimental studies of Pappenheimer. It had not progressed to such a degree as to cause more than slight weakness and had not been suspected during life in either patient. It is of interest that it is neither so chronic as to resemble any of the classical forms of muscular dystrophy, nor so acute as to be accompanied by the inflammatory reaction associated with polymyositis. In view of the prominence of sensory ganglionic degeneration the condition in our cases has more close resemblance to the pantothenic acid deficiency in swine described by Wintrobe and his associates. Since reversal of such degeneration as a result of feeding of pantothenic acid or pyridoxine, or of vitamin E has not been achieved, it is likely that some factor as yet undetermined is the essential defect. Indeed Mitchell (1941) reported the occurrence of a spastic ataxia in pigs fed on diets containing full supplements of yeast ; it resembled that described by Wintrobe and his associates, with similar degeneration in the dorsal roots and dorsal columns. Mitchell was inclined to attribute the disorder to a mineral defect, possibly a lack of copper. We have not found any description of such a combination of dorsal ganglionic degeneration with polymyositis in man.

The few reported examples of neuritic degeneration associated with polymyositis (" neuromyositis ") by Senator and others, reviewed by Lorenz (1898) and Marinesco (1910), have exhibited minor peripheral neuritic symptoms in association with a polymyositis. One of the cases of Lorenz had loss of sensation in the right leg and foot, with hyperæsthesia in the region of the left arm and trigeminal area. There was no indication of widespread ganglionic degeneration. Though Lorenz states that ataxia is a symptom of neuromyositis we have not found it mentioned in the cases of Senator (1888, 1889), Lorenz (1898) or Gwynn and Gordon (1910).

In both our cases bronchogenic carcinoma was present. In Case 1 a seeding of secondary deposit to the cardia of the stomach had occurred, but without interference with pyloric mechanism or structure. In neither case was anæmia or convulsive disorder observed, but our second patient exhibited megacolon. Nevertheless the type of degenerative nervous and muscular affection is entirely consistent with that resulting from metabolic disorder and present changes in man that are comparable to those associated with deficiency in pantothenic acid in swine. Dermatomyositis without ganglionic degeneration has been reported in association with malignant tumour originating in the breast, ovary, and stomach in at least seven instances (Dostrovsky and Sagher, 1946). McCombs and MacMahon (1947) have recently reported dermatomyositis with bronchogenic carcinoma. A number of substances, such as thiopanic acid and phenyl pantothenone, are known to interfere with the biological conjugation of pantothenic acid in metabolism (Woolley, 1947). It is indeed possible that bronchogenic carcinoma produces a by-product with such effect. The close similarity of the condition in the two patients suggests that the coincidence of carcinoma was more than a chance association. Metabolic studies on similar cases in the future are indicated.

Conclusions

Two cases of primary simple degeneration of the dorsal root ganglion cells associated with a primary degeneration of the muscles (" polymyositis ") are described. Both cases presented a spreading numbness and sensory loss of the extremities, in one of the face, without pain but with severe and progressive ataxia. In both instances bronchogenic pulmonary carcinoma was present. The presence of a metabolic disorder related to the tumour cells is presumed, for the neuromuscular condition reproduced changes that have been seen in pantothenic acid and in vitamin E deficiency in animals.

References

Bielschowsky, M. (1908). *J. Psychol. Neurol., Lpz.*, **11**, 188.

Burton, J. A. G., Cowan, J., and Miller, H. (1923). *Quart. J. Med.*, **17**, 103.

De Castro, F. (1932). Sensory Ganglia of the Cranial and Spinal Nerves. Normal and Pathological. Sect. III, vol. 1, in Penfield's " Cytology and Cellular Pathology of the Nervous System." New York.

Demme, H. (1932). *Dtsch. Z. Nervenheilk.*, **125,** 1.
Denny-Brown, D. (1946). *Arch. Neurol. Psychiat., Chicago*, **55,** 171.
——(1947). *Medicine*, **26,** 41.
——, and Brenner, C. (1944). *Arch. Neurol. Psychiat., Chicago*, **51,** 1.
Dostrovsky, A., and Sagher, F. (1946). *Brit. J. Derm. Syph.*, **58,** 52.
Einarson, L., and Ringsted, A. (1938). "Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats," Copenhagen.
Follis, R. H., and Wintrobe, M. M. (1945). *J. exp. Med.*, **81,** 539.
Forbus, W. D. (1926). *Arch. Pathol.*, **2,** 318, 486.
Goettsch, M., and Pappenheimer, A. M. (1931). *J. exp. Med.*, **54,** 145.
Gwynn, N. C., and Gordon, W. (1910). *Lancet*, **2,** 226.
Juba, A., and Szatmári, A. (1937). *Dtsch. Z. Nervenheilk.*, **142,** 28.
Kendall, D. (1939). *Proc. roy. Soc. Med.*, **32,** 874.
Kuré, K., Nitta, Y., Tsuji, M., Siraisi, K., and Suyenaga, B. (1928). *Quart. J. exp. Physiol.*, **18,** 333.
Lorenz, H. (1898). "Die Muskelerkrankungen," vol. XI, Nothnagels' "Specielle Pathologie und Therapie." Vienna.
Marinesco, G. (1910). "Maladies des Muscles," vol. 38, of Gilbert and Thoinot's "Nouveau Traité de Médicine et de Thérapeutique." Paris.
——, and Draganescu, S. (1930). *Dtsch. Z. Nervenheilk.*, **112,** 44.
——, and Minea, J. (1907). *J. Psychol. Neurol.*, **10,** 182.
McCombs, R. P., and MacMahon, H. E. (1947). *Med. Clin. N. Amer.*, **31,** 1148.
Meyenburg, H. von (1929). Die quergestreifte Muskulatur, in "Handbuch der spec. path. Anatomie und Histologie." Albertini and others. Berlin, **9,** 299.
Mitchell, D. (1941). *Brain*, **64,** 165.
Morgulis, S., Wilder, V. M., and Eppstein, S. H. (1938). *J. Nutrit.*, **16,** 219.
Nageotte, J. (1907). *Rev. Neurol.*, **15,** 933.
Pappenheimer, A. M. (1939). *Amer. J. Path.*, **15,** 179.
——, and Goettsch, M. (1931). *J. exp. Med.*, **53,** 11.
——, and Goettsch, M. (1934). *Ibid.*, **59,** 35.
Peters, G., and Scheid, W. (1938). *Z. ges. Neurol. Psychiat.*, **163,** 367.
Senator, H. (1888). *Dtsch. med. Wschr.*, **14,** 449.
—— (1889). *Z. Klin. Med.*, **15,** 61.
Sherrington, C. S. (1894). *J. Physiol.*, **17,** 211.
Swank, R. L., and Adams, R. D. (1948). *J. Neuropathol. exp. Neurol.* (in the press.)
Thomas, A., and Hauser, G. (1904). *Nouv. Iconog. Salpêtriere*, **17,** 207.
Wintrobe, M. M., Miller, J. L., and Lisco, H. (1940). *Bull. Johns Hopk. Hosp.*, **67,** 377.
——, ——, Follis, R. H., Stein, H. J., Mushatt, C., and Humphreys, S. (1942). *J. Nutrit.*, **24,** 345.
——, Mitchell, D. M., and Kolb, L. C. (1938). *J. exp. Med.* **68,** 207.
Woolley, D. W. (1947). *Physiol. Rev.*, **27,** 308.
Zimmerman, H. M. (1943). *Proc. Ass. res. nerv. ment. Dis.*, **21,** 13.
——, Cowgill, G. R., Bunnell, W. W., and Dann, M. (1934). *Amer. J. Physiol.*, **109,** 440.
——, ——, and Fox, J. C. (1937). *Arch. Neurol. Psychiat., Chicago*, **37,** 286.

PHANTOM LIMBS

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INTRODUCTION

The various phenomena which may appear in a phantom limb are so puzzling and their elucidation so beset with difficulty that it is with some hesitancy that we approach the problem. The difficulty is not lessened by the fact that several penetrating studies have appeared recently, notably by Lhermitte (1939) and Riddoch (1941). Close contact, however, with many amputation cases over a long period provided an opportunity to study limb phantoms, and the excuse for this paper must be that our conclusions are in some important respects at variance with those currently held. This study is not a comprehensive review but is limited to those aspects which seem to us to be the more important in illuminating what may be called the physiology of the phantom.

Material.—The observations were made in prisoner-of-war hospitals and camps in Germany in the years 1940–45. The patients were all men of military age, and amputation was nearly always a sequel to gun-shot wounds. The series was, therefore, fairly uniform and the circumstances of a prisoner-of-war life alike for all.

Some three hundred major and many minor amputations were seen. Amputation had been done usually within the first week or two after wounding, but sometimes not for several months and occasionally as late as twelve to eighteen months. The first ninety-eight cases came under our care six months after wounding in 1940. Thereafter, new cases arrived periodically from other campaigns, and in most of them amputation had already been done weeks or months earlier. The majority of observations began, therefore, when stump and phantom had reached a relatively stable stage. Other cases were seen in the early days, and a few studies were made both before and after amputation. Most of the men remained under observation until repatriated one to three years later, thus allowing study of the phantom at intervals through the more important changes in its evolution.

We were much impressed by the men's co-operation in describing their impressions, and somewhat surprised by their ready acceptance of, and indifference to, the phantom, and by its negligible influence on their outlook. Repeated questioning had no effect in focusing their attention on this curious phenomenon, neither had the irksomeness of captivity, nor the close contact of so many victims. All were in the same plight, their morale was high, and they were eager to overcome the disability—all probably important factors in relation to the strikingly low incidence of painful phantom. It is possible that in other circumstances, for example in later life, after industrial and civilian accidents involving compensation, or when vascular disease necessitates amputation, there is more likelihood of pain or other disagreeable features appearing—epiphenomena, as we believe—which may come to dominate the usual mild sensation of the missing part.

It was found that the men varied greatly in their ability to describe the phantom, and also, apparently, to feel it; and in this respect they fall roughly into three groups. (1) A minority, about 10 per cent., of men with alert minds and well marked phantoms who had made original observations (for example in relation to voluntary movement) and could describe their impressions clearly. These were the most instructive cases and provided important clues for our further inquiries. The occasional man with vivid descriptive powers and an hysterical overlay is, with experience, easily recognized. (2) The majority, about 80 per cent., in whom the typical phantom had been so mild and unobtrusive that little thought had been given to it, and it was described in very general terms. These cases gave the true picture of the average phantom, which is painless and never complained of, and they provided statistical confirmation of the main conclusions acquired from individuals in the first group. (3) The remaining 10 per cent., men of poor intelligence, were unable to describe their impressions or to amplify the vague statement that they felt the hand; they provided no useful information.

Only very few, about 2 per cent., asserted they had never felt a phantom. There was no discoverable reason for this absence of what appears to be a natural phenomenon, but it is perhaps remarkable that more did not refuse to believe what they themselves called "imagination" (a notion which is belied by the remarkably similar descriptions of its manifestations); one man, a Scot, steadfastly asserted that his hand was off, that was that, and he refused to believe such nonsense! Officers, on the whole, tended to confuse the issue by over-describing their impressions, and to experience overlay sensations; their descriptions were less useful than the men's simple statements.

Our detailed case notes were unavoidably lost in Germany at the end of the war. This paper has, therefore, been compiled from memory and is merely an outline of the main facts, without, unfortunately, the prepared statistics and illustrative cases and much detail which cannot be recalled clearly. It is, too, a pity that the men's own words, which are the essence of such a subjective study as this, have been lost. Nevertheless, our conclusions are perhaps of interest, more particularly as they were arrived at without much previous experience of the subject and without preconceived ideas derived at second hand.

Scope of Study.—This falls conveniently under three headings: (1) a description of the more important manifestations in the phantom, and a suggested simple classification of the phenomena; (2) a consideration of the possible significance of these phenomena in relation to the physiology of the nervous system; (3) the observed effects of various peripheral operations (for example, neurectomy, re-amputation), and the indications, as regards the phantom, for operation on the stump.

These three approaches, descriptive, physiological, and surgical, are partly interwoven. The descriptive aspect is the most important, and before speculating on the genesis of the phantom or considering surgical treatment it is necessary to appreciate that three fundamentally different types of sensation may occur: (1) the basic tingling of what we call the "natural phantom," which, as will presently appear, is assumed to have an organic basis at a "middle level" (sensori-motor cortex) in the central nervous system; (2) various additional and sometimes bizarre sensations, presumably of psychogenic origin, determined by activity at "highest levels" of the nervous system; (3) a simpler "lowest level" pins and needles sensation excited by mechanical stimulation of a neuroma in the stump. Pain resembling, if not identical with, causalgia may rarely occur in the stump or phantom; we do not recollect more than three or four such cases. The differentiation of these various sensations is an important aim of this paper, but we have also speculated to some extent on their significance.

THE NATURAL PHANTOM

We wish to stress the fundamental importance of the "natural phantom," by which term is meant the almost invariable appearance in consciousness of the missing part. It is a positive sensation, usually described as tingling, or numbness, which is not painful and, indeed, is often referred to as

" quite pleasant." The initial separating off of this almost universal, basic sensation is important, for if it is included together with other bizarre or unpleasant qualities which *may* appear there is danger of confusing qualities which have little in common and whose anatomical substrates in the nervous system are probably different.

This sensation is always stronger than any vague awareness of an intact limb (which, normally, is not consciously felt, at least as a positive sensation). The tingling presumably has an organic basis and depends upon impulses entering at a conscious level. Occurring at first spontaneously, the patient can also, for a time, induce the phantom sensation by merely thinking about it, but in certain circumstances it appears without his thoughts being directed to it.

The form of the phantom is not haphazard but conforms more or less closely to a common pattern which, however, does not reproduce all the amputated parts. The periphery of the limb, such as the hand or foot, and especially the digits, is the strongest and most enduring portion and may be the only part ever to appear, even after removal of a whole limb. The elbow or knee is sometimes present, the forearm or leg rarely, and the arm and thigh almost never.

The hand, as the patient often calls it, when considered in more detail, frequently consists only of the digits, which can usually be identified individually, even if represented only by the terminal pads or knuckles, until they disappear; but the palm, sometimes the wrist (occasionally quite strong), and less often the dorsum of the hand may also appear. As regards the digits, the thumb and index, especially the thumb, are almost always the strongest and most enduring; and in the digits the most noticeable parts are the pads and sometimes the joints. The little finger is sometimes stronger than the middle.

In the foot the same general pattern is found, with emphasis on the great toe, while the second toe is intermediate and the last three toes are very weak, often described as an ill-defined mass, or they may be entirely absent. The instep and heel are moderately strong when present, but the ankle is weak, and the dorsum rarely appears. The forefoot and instep are thus the most obtrusive parts.

The phantom therefore represents only islands and not the whole of the missing limb, and it is usually realized that there are gaps which cannot be felt. Dull, unobservant patients may say they can feel the whole limb, but, when questioned closely, admit they have no positive sensation of the entire limb. Although a well developed phantom is almost always strongest in the digits, there is no strictly progressive diminution in its strength as the stump is approached, for, as we have seen, the digits are not of equal intensity, the elbow is stronger than the forearm, and the palm is sometimes weaker than the wrist. Upper-limb phantoms are, statistically, considerably stronger and more enduring than those of the lower limb. The phantom thus appears to consist primarily of those parts which have the most extensive representation in the cerebral cortex, especially the digits and the joints, but other parts may appear in very vivid phantoms, particularly in the early stages.

The Shape of the Phantom and its Relation to the Stump

No matter how little of the missing limb appears in the phantom and how extensive the gaps, the patient has no difficulty in estimating where the various parts would be if he could feel them, their size and distance from the stump. This faculty enables him to orientate the different parts to each other and to the stump and he can readily demonstrate their attitude on the normal limb; for example, if he feels only the terminal phalanges of the digits after a shoulder disarticulation he can fit in all the unperceived missing parts and can estimate the angle which the several joints would occupy.

The phantom is correctly aligned to the stump with which it moves. In a shoulder disarticulation it moves with the scapula and in a hip disarticulation it is in line with the trunk. Its movement is not impeded by any interposed solid body, through which it can pass without any feeling of obstruction.

The hand usually assumes an attitude of rest, with the digits slightly flexed and abducted, as if holding a large ball. Sometimes the fingers are semiflexed, and rarely they are fully flexed making a clenched fist. The thumb is occasionally adducted and felt to be in contact with the index. The wrist is usually straight. The digits are never straight or hyperextended in an uncomplicated phantom; the significance of occasional bizarre attitudes will be referred to later. The hand is rarely in the position it occupied at the time of wounding. Occasionally the fingers reappear in a different attitude, for example either more or less flexed; and the patient usually says that " the nerves feel more relaxed when the hand is open " at rest, but " feel tightened up when the hand is closed."

The elbow angle is variable. In rather more than half it is flexed at a right angle with the forearm across the front of the chest; in others it is in full extension with the hand down by the side; while, occasionally, it is fully flexed across the upper chest, or partly extended across the abdomen. The forearm is semipronated.

As regards the lower limb, the foot and toes are in the normal position of rest. In at least two-thirds the knee is extended ; in the remainder it is usually flexed to a right angle, but occasionally it is partly or fully flexed.

In fact, the posture of the majority of upper and lower limb phantoms recalls that of hemiplegia. The attitude of the hand or foot is not affected by the level of amputation nor, after shoulder disarticulation, is the angle of the elbow affected by the total absence of its controlling muscles.

Telescoping

This curious phenomenon, in which the digits gradually approach the stump and finally become attached to it, is so common that it must be regarded as a property of the natural phantom. It is associated with, and presumably results from, the general weakening of the phantom. The gaps which remain after the weaker parts have faded out of consciousness (or never appeared in it) retain their normal size for some time before becoming gradually smaller, and even then they do not, as a rule, disappear suddenly. This gradual shrinkage and elimination results in telescoping. It is a diffuse process, affecting most of the limb simultaneously, and not progressively from the stump towards the periphery, and is obviously a further stage of the fading out of the weaker parts.

The time at which shortening begins and the period taken for its completion are variable. The digits may reach the stump in a month or two after amputation or only after several years. The time taken does not appear to depend on the level of amputation, that is, the distance to be transversed by the digits, but, on the whole, it is quicker in the lower limb : a rough average is one to one and a half years for thigh amputations and two to two and a half years for arm amputations. This significant difference is probably related to the relative weakness of lower-limb phantoms. Although the rate of telescoping is not related to the actual distance traversed, it appears to be influenced by the strength of the phantoms of the disappearing segments as well as that of the digits. Thus telescoping was completed in thigh and leg amputations at about the same time (if anything quicker in the former, probably because it is more easily appreciated), but there is a considerable difference in the upper limb : by two years it was complete in almost all lower-limb amputations, in 80 per cent. of forearm, in only 50 per cent. of arm amputations, and in none of the nine shoulder disarticulations although it had begun in all.

Telescoping affects the long segments (proximal and distal) * gradually and simultaneously, but the digits retain their normal size much longer, hence a partly telescoped phantom is often appreciated as a " baby arm with a hand of normal size," or the disproportion may be described by saying the " fingers have become very large." There is a striking difference between the toes and fingers in that the latter are much stronger and retain their outline much longer after telescoping. The fingers are generally normal in size on reaching the stump and can almost always be identified individually ; in the lower limb usually only the great toe remains but has often lost its form and is merely a vague tingling, the other toes having already disappeared or consisting only of an indefinable conglomerate mass.

As a right angle (right) arm phantom becomes smaller the hand gradually retreats from the left side of the abdomen towards the right breast. The hand still retains its horizontal position even when it is just at the stump and the patient appreciates the small space occupied by the elbow and wrist ; then when all has gone except the digits these change direction on becoming attached to the stump and usually hang straight down, but sometimes they curl around the end of the stump as if grasping it. The thumb and great toe are always on the medial side. In at least 10 per cent. of amputations the phantom fingers retract within the lower end of the stump where they can still be identified and sometimes moved, but the much weaker toes very rarely do this.

Observant patients are usually aware of the gradual telescoping, especially in the upper limb ; it is better appreciated after high amputations and when the elbow or knee is flexed—" when I think about it I realize it is short." A poor witness, however, often fails to notice the shortening, even when asked about it, until he suddenly realizes the digits are at the stump. Occasionally, a phantom, especially when only partly telescoped, will lengthen temporarily in response to a strong intensifying stimulus (for example fright) or climatic change, so that the shortening is not strictly irreversible, and a part which had apparently been completely obliterated can reappear, but this ceases to happen soon after telescoping is complete. In rare instances no shortening occurs, especially when severe pain or psychogenic manifestations are present.

The phantom, then, evidently reflects the relative importance of cerebral representation of the different parts of the limb. The loss of anatomical proportion in the telescoping phantom makes it unlikely that appreciation of the phantom depends

* The terms proximal and distal amputation or segment of the limb are used to indicate the arm or thigh and forearm or leg respectively.

upon any visual impression of the body scheme. The descriptions of the telescoping phantom call to mind Penfield and Boldrey's (1937) homunculus depicting cortical representation; but we would make the index finger and perhaps the wrist larger than theirs.

The Course of the Natural Phantom

The phantom is an immediate consequence of amputation and is often perceived when the patient awakens from the anæsthetic; there is nothing unnatural about the sensation and at first the patient may have the impression that the expected amputation has not been done until he discovers that the part, which can be felt so vividly, is absent. At first the phantom is present almost continuously, and some patients, disappointed at losing the limb, may, for a time be obsessed by this strange phenomenon. After a few weeks the tingling becomes weaker, recurs less frequently, and is noticed spontaneously only a few times during the day for perhaps ten or twenty minutes, usually when the patient has nothing to do or think about and especially in the evening when lying quietly before going to sleep after "lights out." It does not prevent or disturb sleep, and is rarely noticed when he is actively occupied.

During the next six to twelve months (it may be a much shorter or longer period) the phantom weakens considerably and its spontaneous appearances become less frequent until it is noticed only once or twice a week, although it can still be induced momentarily by thinking about it. Later it cannot be voluntarily felt (except in distal amputations when it can be induced for a further period by voluntarily moving the digits, as described later). Finally it may continue to appear spontaneously on rare occasions, chiefly in the winter, but this in the average case is so infrequent that after two or three years it may be said to have disappeared. However, this is only partly true of major amputations, for it appears that even after ten or twenty years the natural phantom may still be felt occasionally though never commented on—in contradistinction to painful manifestations which sometimes persist throughout the patient's life.

The average phantom, then, is mild, rapidly subsides, and is soon no longer noticed. If we may speculate, its existence seems to depend upon some change in the activity of cerebral centres, related to the amputated part, which appears to be modified by two opposing influences, the spontaneous activity of the resting brain and the distracting, swamping effect of extraneous activity and thought. The behaviour of the phantom suggests that the spontaneous activity of these cerebral centres is intensified at the moment of amputation and then after a time gradually subsides, so that one part of the phantom fades out after another. It reappears at longer and longer intervals and the various inducing factors (described later) cease to be effective until at last only the stronger external influences (such as voluntary movements or change of weather) are able to revivify the sensation.

The Impression of Voluntary Movement

The impression of voluntary movement, the motor counterpart of the sensory tingling, and other features regarded as part of the natural phantom will now be considered.

Most patients are aware of their ability to move at will certain components of the phantom, especially the digits. These willed or voluntary movements are not haphazard, but conform to certain patterns which partly depend upon (*a*) the level of the amputation, whether distal or proximal, and (*b*) the degree of sensory awareness of the various joints. These motor phenomena constitute an important part of the phantom, and are complementary to, and in close relationship with, the sensory component already described. Their nature shows that they cannot be purely "imaginary" or psychogenic but depend on physiological processes. Moreover, it does not appear to us probable that they are to be attributed to stimulation of nerve endings in the stump.

These movements do not occur spontaneously but require voluntary effort. Dull and disinterested patients, not having made the attempt, have never experienced them, but when asked to try they usually realize the fingers can be moved, although a few seem unable to initiate the movement. Occasionally, total absence of digit movement seems to be due to functional suppression related to the pre-amputation condition of the hand (referred to later).

In forearm amputations, the digits can at first be moved in every phantom. Movement is always restricted, often to one-third or less of the full range, and consists simply of flexion and extension, and flexion is easier and persists longer than extension. Wrist movement requires more effort, is not always possible, is of smaller range, and is confined to slight flexion and extension about equally, though extension is sometimes the easier movement.

In arm amputations and shoulder disarticulations digit movement is more difficult, disappears sooner, and is not always possible. Its range is much smaller than in forearm amputations and flexion is again easier than extension, which latter is done with difficulty "against pressure" and is often

impossible. Elbow movement is rare, and is limited to slight flexion and perhaps a trace of extension.

In the lower limb the same kind of movements occur as in the upper, but, as the phantom is weaker, they are more difficult to produce, are smaller in range, and disappear sooner. In below-knee amputations, there is no striking difference between flexion and extension of the toes or of the ankle. In thigh amputations toe movement is usually a mere flicker. Movement at the knee was observed on even fewer occasions than at the elbow ; it took place always in a flexed phantom and only flexion occurred.

The ability to move the different digits is proportionate to the strength of the sensory tingling. It is freest and persists longest in the thumb, index, and great toe, which can sometimes be moved independently, and it may happen that while all hand digits can be flexed only the thumb can be slightly extended. While movement can still be effected at all joints in the early stages after an arm amputation, the fingers and wrist can usually be flexed simultaneously but not with the elbow ; it appears that when attempting elbow movement the patient thinks of the hand and tries to move its position in space, and not of the elbow which he sometimes " cannot even feel." Essentially voluntary but weak movements such as adduction and abduction of the digits never occur ; neither does inversion or eversion of the ankle which, as naturally occurring movements in the intact subject, are more postural or associated movements than voluntary acts.

Muscle Actions during Voluntary Movements

It is interesting to consider the actions of the stump muscles during voluntary movements within the phantom. These are more conveniently studied in the lower limb because of the simpler innervation and movements, and we had more opportunity of observing the effects of denervation. The below-knee amputation may be considered first.

Every willed movement of the toes or ankle is accompanied by a plainly visible partial contraction of the appropriate muscles in the stump. For example, in suitable stumps the superficial calf muscles can be seen to twitch during ankle flexion and the deep muscles during toe flexion. If the extensor group of muscles is denervated by cutting the peroneal nerve the toes can no longer be extended, but flexion is not affected and when the contraction ceases the toes return passively to the resting position. It is also important to note that the position of the toes at rest remains unaltered, an observation suggesting that the resting attitude of the phantom does not depend upon tonic innervation of the stump muscles or on afferent proprioceptive impulses. If, as a further step, the remaining muscles in the stump are denervated all movement is lost. The same phenomenon occurs in forearm amputations ; for example, denervation of the muscles supplied by the median nerve abolishes flexion of the thumb and index, but not of the other fingers.

From these observations it would appear, (*a*) that the presence of some innervated muscle in the stump is necessary for the performance of willed movements in the phantom, or, put in another way, that the appreciation of willed movements depends on afferent impulses from the muscles which normally move the part ; and (*b*) that the resting attitude assumed by a phantom joint does not depend on impulses from the periphery. The former conclusion is understandable, for it is the normal mechanism of the motor system. It is not enough for the cortex to discharge a motor impulse ; before the phantom toes are felt to move there must be an afferent reply that the muscles have contracted. That this cannot be the whole explanation, however, will appear from the following three observations.

1. Many patients can move the phantom toes but not the ankle although the muscles controlling both joints are present in the stump. This we believe to be due to the relative weakness of the ankle in the sensory phantom, or perhaps, more accurately, to weaker central representation of ankle than of toe movements (even though the muscles concerned are more powerful than the toe muscles).

2. In thigh amputations, in which no toe-moving muscles remain, toe movements are often possible, though small. These toe movements are also associated with a slight twitch in the muscles, which is seen chiefly in the vastus lateralis during extension and the medial hamstrings during flexion, though it is much less than in a below-knee stump. This twitching in the thigh muscles probably represents subsidiary contractions, which occur normally in the more proximal muscles during extensive purposive (digital) movements of the intact limb and have become unmasked by amputation, rather than an acquired secondary motor spread when the principal pathway to the toe muscles no longer exists. Afferent impulses from the slightly contracting muscle fibres in the thigh can evidently be relayed back to the sensory cortex for the toes and the contraction of those fibres is interpreted in reference to toe movement. This, however, happens only in the absence of both the toe-moving muscles and the knee joint, for when a below-knee stump is totally denervated the intact thigh muscles do not

contract vicariously for the paralysed leg muscles and there is no sensation of toe movement ; it may be that the subsidiary arc is then in conflict with, and suppressed by, stronger afferent impulses from the intact stationary knee joint.

3. There is another important anomaly regarding the muscles. It might be expected that in a proximal amputation the presence of muscles which normally control the elbow or the knee would facilitate willed movements of those joints, but this is not so. Voluntary knee movement, through a limited range of perhaps 20 to 30 degrees, still occurs after, say, six months in only about 5 per cent. of thigh amputations. Our few observations during the first three months or so suggest that knee movement occurs more often at first, though never so frequently as toe movement, and it rapidly disappears. We believe that this paradox is due to the relatively small cortical representation of the knee muscles, which are predominantly postural and are concerned with the least voluntary movements in the limb. Voluntary flexion of the elbow is associated with moderate tonic contraction of the biceps, which is greater than the twitching during the easier digit movement.

The progressive spread of motor impulses from distal to proximal muscles is thus unmasked in amputations, possibly because the proximal muscles are released from their distal attachments, thereby allowing contraction in those muscle fibres which are under the more voluntary control. It is clearly seen after a high arm amputation, when flexion of the digits is associated with twitching in the biceps, especially on its medial side, and extension with a flicker in the lateral part of the triceps ; but, if these muscles have been removed in a shoulder disarticulation, twitching then occurs in the posterior fibres of the deltoid.

An interesting observation was made in a man with a high arm amputation who could move the phantom fingers and also, slightly, the elbow. In the course of an ulnar neurectomy for painful neuroma, the elbow flexors were temporarily paralysed by crushing the musculo-cutaneous nerve. This abolished phantom flexion of the elbow, though he could still extend it very slightly and the resting position remained unaltered. Finger movement was unaffected, but the associated muscle twitching was transferred to the posterior fibres of the deltoid ; it returned, however, to the medial part of the biceps a few months later after the crushed nerve had regenerated. A slight spread of contraction to the shoulder muscles is often observed during digital movement in the stronger phantoms after arm amputation and the stump sometimes moves slightly.

We have observed a similar phenomenon in quite different circumstances during a local fit due to a cerebral glioma. The movements were mild, were confined to the upper limb, and consisted chiefly of clonic flexion of the fingers, less of the wrist, and very slightly of the elbow, and, in addition, a little twitching was visible in the posterior fibres of the deltoid exactly as happens during voluntary digital movements after high amputation.

This overflow or spread of impulses from, as Hughlings Jackson (1931) put it, the most voluntary to the most automatic muscle groups, that is, to those muscles least used in initiating voluntary movements, is what happens during the more extensive purposive movements of the intact limb, in which the subsidiary proximal muscles are progressively activated in support of the leading part, the digits. The similarity of the phenomena in local epilepsy to those following amputation supports the contention that the latter are intimately associated with the sensori-motor cortex. Further, this relationship between cortex and limb muscles is indicated by the fact that the fibres which contract (for example, in the vastus lateralis) during the movement of phantom digits are those which are recognized as being more directly under cortical control (phasic fibres) than the more postural fibres in the remainder of the muscle (Denny-Brown, 1929).

Having established an association between the impression of voluntary digital movements and twitching of the stump muscles, it is of interest to follow this relationship as the phantom weakens over the course of years. The range of movement and the muscle twitching both decrease gradually with the diminishing strength of the phantom. There is, however, a striking difference in the relationship of these two motor phenomena to their sensory counterpart, depending upon whether the amputation is through the proximal or the distal segment of the limb. It will be described for the upper limb as the stronger phantom sensations are here more easily appreciated.

In a forearm amputation, finger movement is at first easy and there is considerable, though nothing like maximal, contraction of the associated muscles. At this stage digital tingling frequently appears spontaneously and is easily induced by merely thinking about the phantom, without any thought of movement. Later, after a variable period of say six months to two years, when the phantom has weakened so that digital sensation cannot be felt at will and only rarely appears spontaneously, it can still be readily induced momentarily by moving the fingers and there is a slight muscle contraction ; there seems to be a tingling sensation of the resting

phantom in addition to the sensation of movement, but it is difficult to be certain about this. The ability to induce movement persists for a long time, and in the few cases in which it had disappeared by two to three years the muscles had also ceased to contract. These patients often say in the later stages that they " never feel the fingers except when moving them." As the range of movement fades to nothing, so the muscle contraction disappears and the phantom fades out.

In an arm amputation, on the other hand, the muscles have much less influence in inducing the phantom. In the early months the strength of the digits, and the tendency for them to appear spontaneously is much the same as in forearm cases, but the ease and range of movement and the degree of twitching in the stump muscles is considerably less. As the phantom weakens, voluntary movement rapidly becomes " more difficult," " the fingers are slower and stiffer than they were," and he has " to work harder to move them." We gained the impression from some cases that the muscle contraction increased for a period, probably due to the extra effort required to move the digits and especially the wrist. But a stage is soon reached, at perhaps twelve to eighteen months, when the ability to move the fingers has gone, although the sensory phantom still appears quite plainly, and " the fingers have become locked " or " the fingers seem to be held firmly in a vice " (but without discomfort). In a weakening phantom the increased effort to move the fingers in the later stages often seems to increase the tingling, presumably due to intense concentration. Slight muscular twitching continues, however, often for many months after the cessation of digit movement ; it would seem that the afferent impulses from the later twitchings in these subsidiary muscles become too weak to attain the necessary threshold in the related sensory cortex.

In proximal amputations it seems that for a period after the ability to move the digits has apparently ceased, when " the great toe is very stiff—I don't feel it enough to move it "—it is possible by continued concentration for a minute or two to overcome the stiffness slightly, when " it seems the great toe is loosening up a little " and can be moved slightly. It is likely that the simultaneously increased tingling also results from the concentration—a kind of facilitation.

Voluntary movements thus disappear some time before the sensory tingling (and often before the digits reach the stump) in proximal amputations, but not until a considerable time after it in distal amputations. There is, however, no essential difference in the length of time before the spontaneous tingling disappears. The distal muscles, therefore, have an important influence on the phantom, in that they remain the only means of inducing it for a time after it has faded from consciousness. During this period the phantom must still exist at a subconscious level, otherwise the motor mechanism could not function in relation to it and could not revive it. This ability of willed movements after a distal amputation to induce a sensation of the phantom when it is no longer possible by merely thinking about it again suggests that the phenomena of the natural phantom are more closely related to the sensori-motor cortex than to higher centres.

The relationship of willed movements to the sensory side of the phantom is well brought out by the patients' observations when attempting to move each of the three groups of joints at a suitable stage in the life of the phantom. They often say they can move the fingers easily, the wrist with much greater difficulty, and the elbow not at all. When pressed about the inability to move the elbow they reply that they " cannot feel it and don't even know there is an elbow and it is no good trying," or, that they " do not know how to go about it," in spite of having been able to do so at an earlier stage. The freedom of movement, however, depends not only on the sensory awareness of the part, but also (and perhaps chiefly) on the sensory representation (and voluntary control) of the movements concerned ; finger flexion is easier, and has more extensive cortical representation, than extension, even though the muscles effecting both movements are present in the stump.

The fact that the biceps contraction is smaller during digit movements than during the more difficult elbow movements is perhaps evidence of the more extensive central representation of the former. The importance of afferent impulses from contracting muscle on the freedom and range of movement is shown by the greater degree present in distal amputations ; but the fact that voluntary movement persists in the digits after it has disappeared at the wrist shows the over-riding importance of central threshold levels.

The last and perhaps the most curious fact is that after the disappearance of willed movements some of the central connexions for innervation of the stump muscles continue to function, for when the patient is asked to " work the *muscles* " in the stump as much as possible, a maximum contraction is easily produced, but it has *no* effect in moving the elbow or other joints, nor, indeed, of inducing any sensation of the phantom.

These observations, then, appear to show that : (1) to initiate willed movements in a phantom the motor cortex must first receive guidance from the sensory cortex in which the particular movement is

still represented consciously or subconsciously; (2) the highest centres can activate stump muscles by two routes: (*a*) via the sensory cortex, when the muscle contraction and the joint movement in the phantom are never maximal and both gradually decrease and eventually disappear; (*b*) by a more direct route without the controlling influence of the sensory cortex, when the contraction is maximal, produces no sensation of the phantom, persists after the phantom has disappeared, and does not diminish with the passage of time; (3) proprioceptive impulses from muscles do not initiate willed phantom movements, for these are a function of the sensori-motor cortex, but they are essential for the registration of the impression of such movements; (4) the phantom shows clearly that proximal and distal muscles are under different nervous control.

Automatic Knee Movements

An interesting fact concerning knee movement, though not voluntary movement, may be mentioned here. More than 10 per cent. of patients had observed that the phantom knee sometimes moved spontaneously through as much as 90 degrees, but "it is just automatic." This type of movement, which results in the knee being "sometimes straight and sometimes bent," occurs in various circumstances, such as: (1) during a change of body posture, for example, a knee which is straight when the patient is recumbent may bend to a right angle when he sits on the side of the bed so that the foot appears to hang down, or when he turns on his side in bed with the normal leg flexed so that "the legs are alike"; (2) as a visual reflex, for example, when the patient is walking on crutches the knee may automatically flex about 45 degrees if there is an obstruction in the path of the untelescoped phantom foot, or, again, to avoid hitting the steps when climbing stairs, but not when descending. These automatic changes of attitude within the phantom, in which a new position suddenly appears, cannot be voluntarily initiated or prevented, are instantaneous, and the movement is never noticed; attempts to observe the stump muscles during the movement were unsatisfactory. They have no connexion with voluntary knee movements (although the toes can usually be moved) for patients say that "the knee cannot be moved except when it moves itself."

Automatic movements did not occur at the distal joints and only rarely at the elbow and then chiefly when in bed. They evidently reflect the normal, more automatic control of the predominantly postural muscles in the thigh, and may be mediated through reflexes at a lower level in the nervous system than those concerned with the sensory phantom and its voluntary movements.

The change of position which enables the phantom foot to avoid an obstruction can hardly be due, as has been already pointed out, to an inability of the phantom to enter a solid body; were it so the attitude of the phantom would be constantly changing, either at a joint, which rarely happens, or where the phantom joins the stump, causing it to lose correct alignment, which never happens.

Yet another observation, which seems to concern a mechanism intermediate between voluntary and automatic knee movements, was made by a few patients who noticed that if they "tightened" the knee they could feel the patella tighten and move slightly upwards; this was associated with a prolonged moderately strong tonic contraction of the whole quadriceps, but there was no movement of the phantom knee.

Involuntary Spasmodic Movements

Involuntary spasmodic movements, which are often painful, will be referred to later. They are regarded as an overlay, functional manifestation, without any relation to sensori-motor cortex.

Factors affecting the Appearance and Strength of the Natural Phantom

1. The Stump.—Pain in the stump merely overshadows the perception of the phantom, and hence during healing may delay its appearance for several weeks, or later, during recurrent inflammation, cause it to disappear temporarily. Attention is also diverted from the phantom by severe pain elsewhere. Mechanical stimulation of the nerves does not affect the intensity of the natural phantom, and trauma has no effect beyond making the stump painful. Contraction of healing muscles causes discomfort and is automatically avoided, so that it is generally a month or two before digit movement is tried and appreciated.

Local conditions in the stump have little other influence, apart, of course, from the possible appearance, after some months, of a superficial sensitive neuroma, stimulation of which causes a pins and needles sensation. A neuroma also leads to the avoidance of voluntary movements when the associated muscular contractions irritate it. On the whole, the length of stump and the method of amputation, whether by guillotine (as in the majority of these cases) or by flaps, made no difference to the phantom, nor, so far as we could tell, did the method of treating the divided nerves. Infection, even when prolonged, had no intensifying action on the phantom. The effect of a persistently unsatisfactory stump in causing dissatisfaction and unpleasant overlay manifestations, and also the rare occurrence of causalgia, are discussed later.

2. Sedatives, Shock, and Toxæmia.—These, by lowering the level of consciousness, delay the appearance of the phantom.

3. Climatic Conditions.—The weather has a marked influence on the vast majority of phantoms, in that they

are more noticeable in winter, especially during a cold or wet spell. This is the most enduring influence, and it persists long after other inducing and intensifying factors have ceased to be effective. After two or three years the phantom may be noticed only when there is " a change in the weather," or when it is very cold.

4. Thinking of the Phantom.—The patient can at first evoke the phantom, temporarily in abeyance, by merely thinking about it. This voluntary direction of thought is, like other factors, at first uniformly effective but it gradually becomes weaker and finally disappears. It is one of the more enduring influences but it is significant that the patient cannot even imagine he feels the phantom in the later stages, which shows that, like the more obviously reflex factors, it too depends upon, and is influenced by, changes of an " organic " kind.

5. Micturition and other Visceral Reflexes.—These have received passing mention from most writers. There is a brief sensation in the stump or in the phantom during micturition in at least 90 per cent. of thigh and leg amputations alike, during defæcation in about half the cases, and occasionally in association with the passage of flatus. It is usually mild and almost unnoticed ; in fact, more than twenty patients had been seen before it was mentioned casually although, on requestioning, it was found that nearly all had experienced the sensation.

The sensation induced is one of two kinds : (1) a tingling in the phantom and conforming to it as regards position and telescoping ; (2) a tingling on the end of the stump, without any reference to the phantom which still retains its normal or partially telescoped position. The sensation sometimes begins by shooting down the stump, perhaps only the last few inches, but occasionally from the groin. The effect is the same with micturition and defæcation, and it appears to remain constant for the individual, as we do not recall a change of response from phantom to stump, although, in this connexion our observations were few.

The tingling has a constant time relationship in the act of micturition. It appears just as the bladder releases and the flow starts. Its duration is variable but is usually short, often only momentary, and almost always fades away before the bladder has half emptied. Distension of the bladder sometimes has a similar effect when the appearance of tingling draws attention to a full bladder, previously quite unnoticed. In such cases its intensity increases until the bladder empties, though there is, in addition, a momentary intensification as the flow starts.

The strength and persistence of the micturition phenomenon varies greatly from case to case. Not uncommonly it is stronger than the spontaneous phantom during the first few weeks and may even be the only manifestation of a phantom, but it rapidly fades and is soon weaker than the spontaneous tingling (which has perhaps become more noticeable). In some it is very weak and fades out within a few weeks, in the majority it is mild and persists for several months or even into the second year, and occasionally it is truly painful, so much so that micturition is dreaded, indicating, we believe, individual variations in the threshold to pain.

A similar sensation commonly accompanies defæcation just as evacuation begins, and, as with micturition, is either in the phantom or in the stump. When both micturition and defæcation responses occur, the former is usually the stronger and more persistent, but either may occur alone. It is difficult to assess the importance of straining. Many say the effect is stronger during constipation, but it seems that the sensation usually appears just for a moment as the sphincter relaxes and does not persist during defæcation, nor is it present during preliminary straining. Nevertheless, it is likely that previous visceral distension increases the response, for the micturition effect is often said to be strongest in the morning, especially if the bladder is distended on wakening, and the defæcation response during periods of constipation.

In upper limb amputations the effects just described never occurred, but in a few cases, less than 20 per cent., a momentary phantom sensation was induced in other ways, for example : (1) during the act of swallowing very cold water, or more rarely in other individuals, very hot water (retaining it in the mouth had no effect), and occasionally when yawning ; (2) washing the same side of the face, neck, axilla or upper chest with cold water ; (3) shaving the same side of the face or neck. Performance of the last two acts was occasionally very unpleasant. The sensation, unlike that in the weaker lower limb phantoms, nearly always begins by running down the stump usually from the shoulder or lower part of the neck, and may, or may not, continue into the phantom.

6. Muscular Action.—The effect of the muscle twitching associated with voluntary movement of the digits in reviving a disappearing phantom has already been described.

7. Loss of Balance.—When the patient stumbles or slips on crutches a strong sensation shoots down the limb, the phantom is felt momentarily, and simultaneously the stump moves out as if to save the patient from falling. Later, the stump may move without any sensation of the phantom. This is one of the more enduring reflexes and generally persists for a year or two. It is interesting to note that the movement of the stump usually changes from putting it out as if to stand on the foot to flexion of the thigh in order to avoid injury to the end of the stump in falling.

8. Instinctive Actions.—It is quite natural that, for a time, the missing part should seek to take its place along with the other limbs in the performance of more or less automatic every-day actions, as in dressing, using the hand to pick up objects or catch a ball, stepping out of bed on the missing foot, crossing the knees with a thigh stump, or, while in bed, moving the stump if anyone is about to sit where the foot appears to be. When the stump begins to move the mistake is realized and simultaneously there is often, but not always, a momentary sensation of the phantom. Individuals vary greatly in this tendency to use the missing limb and some assert they never did so. These instinctive actions generally cease after a few such incidents, usually within a few months, for the patients " quickly learn to avoid making mistakes."

It is interesting to speculate why in these instances the network of central activity concerned in simple, subconscious, and more or less automatic actions involving centres for several limbs should evoke a conscious sensation in the sensory cortex related to the amputated limb and not elsewhere. Is this cortex in a hypersensitive state, enabling the normally subconscious reflexes locally to reach a conscious level?

The sensations during instinctive actions are weaker and disappear sooner than those associated with the fright of falling, as would be expected, for the intensity of reflex action may be presumed to be considerably less. The reason why mistakes soon cease to be made may depend upon re-education, as these reflexes are initiated centrally and presumably at a higher level than those in response to fright, and overbalancing, which are induced by peripheral stimuli and are therefore more automatic.

9. Vision.—Vision sometimes provides an effective stimulus, for example, seeing a man with an amputation may cause the phantom to appear. The occasional adoption by the phantom of the position in which the limb had been splinted before amputation (described later) probably depends on vision more than other sensory impressions. Also, it seems to provide the stimulus for some automatic knee movements. The chief importance of vision, however, is its effect in modifying the natural phantom by suppressing part of it or by adding sensations, for example, superimposing the visual impression of the original wound (described later). There is no evidence that vision is fundamentally concerned in the genesis of the phantom phenomenon, which appears in similar form in men who have been blind from the time of wounding.

10. Fright.—A sudden fright, for example, from a loud noise, is sometimes associated with a momentary sensation of the phantom. Fright probably plays a part in the reaction to falling.

11. Emotion.—Emotion such as anger or excitement makes the patient forget the phantom.

12. Learning to Write.—This never induced the phantom, except in two strongly left-handed men with left-arm amputations.

13. Wearing an Artificial Limb.—Wearing and walking on an artificial limb has a striking effect. Nearly a hundred men were fitted with temporary, above- or below-knee, wood-plaster limbs nine to eighteen months after amputation, which enabled them to get about again without crutches and usually without sticks. Almost without exception the phantom was never felt while wearing the prothese but often reappeared when it was removed. This effect may be partly psychological due to greater freedom of locomotion, but it is likely that other factors are important. It was, for instance, sometimes observed that, when the patient was standing, if all the body weight was transferred to the normal leg, and the stump was slightly lifted out of the socket, the phantom appeared, but it disappeared when the patient was standing equally on both legs. It was not noticed when walking. Similar observations suggest that in the upright posture correct distribution of body weight, balance, and the automatic actions in walking may have an important inhibitory effect. We had no experience of artificial arms.

14. Time of Amputation.—There was no noticeable difference in phantoms following amputations done at the time of wounding, or within a few weeks or months. Phantoms did not appear, however, in several cases of late thigh amputation, done eighteen months to two years after wounding, with co-existing complete sciatic nerve lesions in which the total loss of sensation in the anterior half of the foot was verified before operation. As the usual lower-limb phantoms have often disappeared by eighteen months, the question arises whether the non-appearance of a phantom in such cases can be attributed to the fact that the cortex had already long been deprived of its normal sensory connexions in the sciatic territory, especially the forefoot; in other words, whether denervation has an effect similar to amputation on the cerebral cortex, except that after peripheral nerve injuries the presence of the foot in some way inhibits the appearance of a phantom.

Relation of the Phantom to Solid Structures

One of the most striking and curious features of a limb phantom is its ability to pass through solid structures unimpeded and without arousing any feeling of obstruction or unpleasant sensation. Its behaviour in relation to solid structures may be considered under three headings:

1. The relation of the whole phantom to the patient's body. The phantom always moves in alignment with the stump, so that a hand which is normally in front of the trunk can be made, by moving an arm stump backwards, to pass straight through the patient's body.

2. Its relation to external objects. Again, the phantom maintains its shape and its relation to the stump, and ignores the presence of an obstruction, so that it goes through, for example, a wall or a table. When in bed the foot of a right-angle phantom appears below the mattress, but if the knee is only slightly flexed the foot is felt to be inside the mattress.

An interesting phenomenon was met with in several cases, in all of which the fingers were fully telescoped and projected downwards from the end of an arm stump. When the stump was slowly approximated to a wall, the fingers seemed to enter it (the wall) and nothing happened until the stump touched the wall when they were instantly displaced either sideways or inside the lower end of the stump, as if they had been pushed backwards. It made no difference whether or not the patient was watching and there was no associated pain or other sensation. When the stump was removed the fingers instantly returned to their former position. This effect was

not observed when telescoping was incomplete nor in the lower limb, possibly because the toes are weak and have often disappeared before reaching the stump.

The only change that occurs, then, in these two groups is when strong phantom digits, attached to the stump, appear to occupy a space which, according to the normal sensory impulses from the end of the stump, does not exist. In this conflict the normal cutaneous sensory information prevails and the fingers are displaced into the stump without any sense of resistance, as sometimes occurs spontaneously in the natural course of the phantom. It is strange that, apart from this special circumstance, the phantom, which seems to maintain such perfect connexion and harmony with the stump, can yet be so detached from the patient and from external reality. The fact that it ignores other (normal) impressions, bodily or visual, may be due, in part, to weakened central neuronal connexions representing the gaps in the untelescoped phantom, and possibly in part to the active digital cortex taking precedence over other (for example, visual) impressions. The only exception is when the fully telescoped fingers become so to speak part of the stump and the normal cutaneous impulses are in direct (anatomical) conflict with the abnormal impression of the digits which have to give way. But most interesting is the ability of the normal stump to engulf the phantom digits, temporarily or permanently.

3. The relation between different parts within the phantom. Occasionally the attitude of the hand is such that one part feels to be firmly in contact with another and may dig into it, for example, the tip of the adducted semiflexed thumb pressing against and piercing the lateral side of the semiflexed index ; or, the palm is felt because the nails of the fully flexed fingers are digging into it ; or, in the mildest cases, there is merely a sensation of light contact between the tips of the semiflexed, opposed index and thumb. Such impressions of contact, and even penetration, are often uncomfortable and have a burning and sometimes very painful quality. They can occur when all the muscles directly concerned are missing, as in arm amputations, and it is difficult to see how irritation of divided afferent nerve fibres from those muscles or of pain fibres could arouse such complex sensations. This is the only circumstance in which a part of the phantom feels to make any contact, namely, with another part of itself, and in which there is an accompaniment of pain which is more severe when the pressure is unusual. These considerations suggest that the sensations probably depend on psychogenic factors.

Increased Tone in the Muscles controlling the Stump

It is interesting to note that in most cases there is an increase of tone in the muscles moving the stump during the induction of general anæsthesia. This excessive tone affects principally the flexors and is manifested either in spontaneous movements of the stump alone or by its exaggerated movement when all the limbs move. It can be demonstrated, in the absence of spontaneous movement, by passively abducting an arm stump which induces clonus. This movement during operations on the stump, when the patient is not fully anæsthetised, is annoying to the surgeon, and it was this that first drew our attention to the phenomenon.

The reason for the increased tone in the muscles controlling the stump, which is in excess of that occurring simultaneously in the normal limbs, is not clear, but two possibilities suggest themselves. It may be an expression of heightened activity in the related centres (for the muscles moving the stump), associated with that in the adjacent cortex representing the amputated part ; or, it may be a release phenomenon, distinct from that which removes higher control during induction of anæsthesia. Is it possible that the tone in proximal (supporting) muscles is normally under some inhibitory control from the distal (leading) part of the limb ? In other words, does a mild release phenomenon with increased tone result from cutting peripheral nerves distal to the muscles (though less than that after isolating them from cerebral control in upper motor neurone lesions) ? If so, this might be regarded as the motor counterpart of the sensory phenomenon which expresses itself in tingling.

It is probable that this increased tone is related to the well known spontaneous jumping of the stump during the early weeks after amputation. It may be that these occasional jerkings of the stump, often amounting to clonus, are sometimes initiated by mechanical irritation of the divided nerves, but a similar quivering occurs reflexly in response to other stimuli such as a fright or during a yawn or a stretch ; also, it frequently happens in the absence of any obvious reflex cause as when the patient is lying quietly in bed especially just before or after falling asleep. There is considerable individual variation in the severity and duration of this jumping, but it gradually subsides and usually disappears within a few months ; in the early weeks it is sometimes associated with a momentary sharp or cramp-like pain in the stump muscles but without a phantom sensation. We regard it as a motor manifestation of the natural phantom which

gradually weakens just as the sensory counterpart, though it often continues to be revealed during induction of anæsthesia.

Excessive Sweating in the Axilla

This occurs after some forearm and most arm amputations, and without any painful or causalgic manifestations. It gradually decreases but may continue for two or three years, and it is sometimes so marked that perspiration is continually running down the chest wall, occasionally even in cold weather and although the other axilla is dry. It is more frequent and more marked the more proximal the amputation. It is regarded as an expression of heightened cerebral activity affecting the sympathetic system and comparable to phantom tingling and stump clonus.

So far only manifestations which are regarded as part of or associated with the " natural phantom " have been described, but others which may be superimposed remain to be considered. Such additional features are present in only a minority of cases, are peculiar to the individual patient, and do not constitute a fundamental part of the phantom. They are, however, sometimes unduly conspicuous and troublesome, in consequence of which, from the standpoint of phantom physiology, undue attention has been given to them in the past, and there has thus been a tendency to think of phantoms generally in terms of these uncommon manifestations. Reference to a disproportionate number of these patients to illustrate the different effects gives a false impression of their frequency, but not, of course, of their importance, for therapeutically these are the only features that matter. The effects to be described come from two entirely different sources, one from stimulation of nerve ends in the stump—the most simple organic manifestation—and the other of psychogenic origin depending on the highest cerebral levels—the most complex phenomenon.

THE NEUROMA SENSATION

It has long been surmized that the various sensations which constitute the phantom are closely connected with afferent impulses originating in the stump. We believe that the only sensation (apart from the impression of voluntary movement) which can with certainty have such a peripheral origin is that resulting from mechanical stimulation of a neuroma. It may be, however, that the occasional spontaneous, momentary sensations, usually mild but sometimes stronger and even knife-like, and localized to small areas in the phantom, are due to irritation of individual fibres in the divided nerve; they are most noticeable during the first month or two after amputation and then gradually disappear.

Although a neuroma forms on every divided nerve, only those situated superficially are liable to repeated trauma. Percussion produces an instantaneous sensation of " pins and needles " which is referred to the cutaneous distribution of the nerve but is always easily differentiated from the tingling of the natural phantom, for it is much stronger, is only momentary, and never occurs apart from mechanical irritation. The distinction is well brought out by stimulating an ulnar neuroma, when the pins and needles in the little finger is in sharp contrast to the tingling in the phantom index and thumb; but even with a median neuroma the patient has no difficulty in distinguishing the two sensations. Further, stimulation of a neuroma has no effect in intensifying or inducing the phantom, which is, indeed, unaffected by troublesome neuromas. Excision of the neuroma, or division of the nerve, abolishes the sensation, but the phantom tingling is unaffected. It seems, therefore, that impulses from the exposed axons, at least those resulting from mechanical stimulation, have no part in the genesis of the natural, spontaneously-appearing phantom. Furthermore, the neuroma, which takes several months to form, cannot be responsible for the phantom which appears immediately after amputation.

It must, however, be emphasized that the sensations of the natural phantom and of the neuroma response, though quite distinct in character and presumably also in origin, have an important mutual relationship in that the latter is always located correctly within the phantom as regards position and degree of telescoping, even when the fingers have retracted within the stump. There must, therefore, be some integration at a high level in the nervous system. After the digits have lost their definition, the neuroma response is referred to the skin on the end of the stump, where it produces simply a pins-and-needles or weaker tingling sensation without reference to digits, and this persists after the phantom has disappeared.

The sensation, strong at first, gradually weakens, but the effect of stimulating the main nerve trunks to the digits never disappears even after the phantom has faded out; on the other hand, the smaller cutaneous nerves, such as the external cutaneous or the branches of the femoral, produce a much weaker response which is at first referred correctly to the phantom, but weakens rapidly as the phantom shortens, and, after being referred to the stump for a short period, disappears even before telescoping is complete. Thus, the sensations from even the poorly represented long segments of the limb are

referred to the normal skin on the stump for a short time before they disappear. Moreover, sensation induced by stimulating nerve ends of greater and of lesser sensory importance when the phantom is partly telescoped may at the same time be referred to the phantom and to the stump respectively. This difference of effect is presumed to depend upon a gradual change (? lowering) in the level of cortical activity affecting unequally the strongly and poorly represented parts.

In some amputations, mostly of the arm, the neuroma is unusually sensitive and produces an excessively strong pins-and-needles sensation, sometimes referred to as pain, which extends proximally up the stump. This recalls (*a*) the inclusion of phantom digits within the stump, and (*b*) the passage of sensations, induced by certain reflexes previously described, from shoulder or groin down the stump before entering the phantom (micturition effect). It may be that the three phenomena are due to the same central mechanism.

The neuroma response is the same sensation that underlies Tinel's sign, but in amputations the peripheral reference is modified by telescoping, which never occurs in peripheral nerve injuries.

MODIFICATION OF THE PHANTOM FROM A HIGHER CEREBRAL LEVEL

The phantom is sometimes modified in such a manner that it is reasonable to assume it is dominated by a higher level than the sensori-motor cortex. In the majority of such cases the natural part of the phantom is unaffected and there are mild superadded sensations which derive chiefly from the memory of previous experiences. In others, the additional sensations are stronger and perhaps painful, or the underlying phantom is itself modified, either by suppression or by distortion into unnatural forms. In the rare, most severe, cases the superimposed sensations may be extremely unpleasant and painful, dominating the phantom and causing the patient to complain bitterly about " the nerves."

We are well aware that we are here about to embark on a highly controversial aspect of the physiology of phantoms, and that many of the phenomena now to be considered have by many been regarded as arising from purely peripheral nerve irritation. Whilst we in no way wish to deny the role of peripheral nerve ending in the genesis of certain types of pain in stump and phantom, we feel, nevertheless, that the probability of a central origin for some at least of these superadded sensations has never received adequate consideration.

Superadded Sensations of Pre-amputation Impressions

The majority of these sensations can be traced to impressions received originally via the sensory system, though in some instances vision may have participated. They are, therefore, a recrudescence of pre-amputation experiences peculiar to the patient and must be distinguished from the basic tingling that is common to all. Brief consideration of their qualities and the factors associated with their development brings out some interesting and suggestive facts.

The sensations may be divided into three groups, depending on the relationship of the parent sensation to the time of wounding : (1) the revivification of a sensation experienced in the limb before wounding, sometimes even several years previously and apparently forgotten, for example, the discomfort of an ingrowing toe-nail or a corn, compression of the toes in a tight boot, the impression of a split finger nail, a painful whitlow, the sensation of a finger ring ; (2) the wound itself ; (3) the persistence of a sensation experienced between the times of wounding and amputation, a period often of several weeks or months duration, for example, the pain of suppurative arthritis, the sensation of a traction pin, pain in relation to pressure points and splints, the sensation of lice crawling under a plaster.

We believe that all these sensations, to which the adjective " superadded " is applied, show features which distinguish them from the pure phantom. They are noticed only occasionally and are mild and transient, usually only momentary in comparison to the more persistent awareness of the natural phantom, and they disappear early. They often appear in the absence of phantom tingling, for example, the ingrowing toe-nail sensation may be present without toe tingling, or a wound sensation be isolated in the gap representing the forearm. Their position in the phantom, however, is always consistent with its shape and telescopic shortening.

A fact of considerable interest, and one that appears to be at variance with the views of many, is that their occurrence had no relation to the intensity of the pre-amputation sensation. For example, in several cases of delayed thigh amputation a slight momentary pain felt in the knee at the time of wounding appeared in the phantom, whereas the later, much more severe and persistent pain of suppurative arthritis in the knee did not. Analysis of about ninety thigh amputations, of which some thirty followed acute arthritis of the knee, often after many weeks of severe continuous pain, showed that it appeared in only a minority of the phantoms, and then usually when the patient had some cause

for dissatisfaction. It is, in fact, our strong impression that a man who has had much pain and who is glad to have the leg off has no pain in the phantom.

A somewhat related fact is that wound phantoms were more common in the lower limb, although the phantom tingling was more vivid in the upper. This apparent anomaly is perhaps due to the more immediately disabling effect of a lower limb wound and the resulting greater mental impression. In the few upper-limb phantoms in which a sensation of the wound appeared, the patients invariably gave a strikingly graphic description of its appearance with details of blood running down the arm, etc., whereas in the lower limb the sensation was simply that of the pain experienced at and shortly after the time of wounding.

The frequency with which a psychologically important sensation persisted in the phantom was quite impressive, and the following example illustrates clearly this association. A soldier in jumping from a truck sprained his ankle. This caused him to fall behind his companions. A few minutes later he was wounded in the same leg just above the ankle, and the pain of the sprain was replaced by a different pain in the wound. He was taken prisoner and a few days later the leg was amputated. He had a typical mild phantom but he noticed principally the pain on the outer aspect of the ankle similar to that caused by the sprain. In the course of the examination he remarked significantly that he would have succeeded in escaping had it not been for the sprained ankle.

These facts suggest that the genesis of this class of superadded sensation is the effect of a psychologically important pain and is not related to the severity and duration of the pain. The slight pain at the time of wounding which is the primary cause of the soldier's troubles, and, in our cases, of his becoming a prisoner of war, is more apt to appear in the phantom than the later severe pain of suppurative arthritis, which is merely an incident in treatment. In other words, the appearance of such superadded sensations probably depends largely on psychological factors.

The Possible Modifying Influence of Pre-amputation Posture

The reason why the elbow or knee is straight in some cases and flexed in others is not clear. After some delayed amputations the attitude of these joints reproduced the position of the previously splinted limb—the patient usually volunteered this information. This was seen most clearly in a small group with the knee slightly flexed at about 135 degrees, almost all of whom had been splinted on a Braun's frame for several weeks or months; or, again, in cases with a fully flexed elbow after the limb had been splinted in that position. Occasionally it corresponded to the position of the limb when wounded; for example, a truck driver with a slightly flexed phantom elbow had been holding the gear lever. The rare cases with full flexion of the knee are harder to explain, though some of the patients, for example miners, said they had normally worked in that attitude. There can be little doubt that some impressive pre-amputation position, especially when acute or obtuse-angled, can modify the attitude of the phantom.

In the large majority of cases these joints adopt an attitude either of full extension or of right-angle flexion. Statistically, there is no apparent relationship to the previous position of the splinted limb, or even to the patient's recollection of the injured limb when wounded or, later, on the stretcher before an immediate amputation; it was the same in some but not in others. Further, it must be uncommon for a lower limb to be splinted with the knee at a right angle, and some patients were unconscious or too shocked to appreciate its position. In the majority of phantoms, the knee was fully extended and the elbow was flexed at a right angle. This is the attitude characteristically adopted in hemiplegia, and we are tempted to see in it the reflection of a postural pattern in the central nervous system. Denervation of one or both groups of stump muscles had no effect on the attitude of the resting joint, which seems to indicate a fundamental cerebral control of the position of joints. If, as we suppose, the relative complexity of voluntary movements is proportionate to the degree of their cortical control, may not the attitude of proximal joints be assumed to represent a lower level central control of postural tone (just as automatic knee movements are supposed to reflect low level reflex movements)? But this leaves unexplained why some elbows are extended and some knees are flexed, without even any apparent relationship to previous posture.

We do not agree with the view that it is the rule for pre-amputation pain and posture to be "frozen" or perpetuated in the phantom. When an unusual sensation appears in a phantom it represents a previous psychologically important experience more often than an immediate pre-amputation "frozen" sensation.

Suppression of Part of the Natural Phantom

This results chiefly from previous visual impressions and affects either the sensory or the motor component.

For example, an airman, severely wounded in the foot, had the leg amputated a day or two later. The phantom was quite typical except that he had never felt the first two toes nor the medial border of the foot, which is normally the stronger side, but he could feel the lateral part of the foot and toes easily. The explanation of this curious distribution appeared when he remarked that he had seen the foot before amputation and remembered clearly that its medial half " had been shot away leaving a gap."

Another example is that of a soldier whose second toe was removed together with the distal part of the metatarsal a few days after being wounded ; this left a " V-shaped gap " which he had seen during dressings. Several weeks later it was necessary to amputate through the leg. The usual phantom appeared in which he could feel all the toes except the second and the V-shaped gap which was " missing." (He could still feel the phantom eighteen months later when the posterior tibial nerve was divided for a painful neuroma ; the whole phantom unexpectedly disappeared completely immediately after this peripheral operation and had not re-appeared during the following twelve months—this case is referred to again in connexion with operations.)

Not only may the tingling of the natural phantom be completely suppressed in a defined area in accordance with a psychologically-important pre-amputation impression, without affecting the remainder of the sensory phantom, but, on the motor side, voluntary movements may also be suppressed locally.

For example, a man with a forearm amputation had an ordinary phantom in which he could feel all the digits and could voluntarily move all except the ring finger, which remained rigid in its slightly flexed attitude, although the stump muscles twitched as usual. The explanation became clear when he remarked casually that the finger had been stiff since an accident several years previously.

A further example is that of a man, seen two months after an arm amputation, in whom the fingers were in the semi-flexed clawed position that they were in when he was wounded (he was holding on to a gun rail). They could not be moved, whereas he could move the wrist slightly and, with greater difficulty, the elbow. Attempted finger movement caused a cramp in the stump muscles, but there was an associated twitching in the muscles just as during movement of the wrist and, in greater degree, of the elbow. The motor phenomena were thus normal apart from the suppression of afferent impulses from the contracting muscles, over which the impression of tightly grasping the gun rail prevailed.

This phenomenon of suppression occasionally affects the whole phantom, as when it totally disappears following an operation on the stump (referred to later). It may also be the explanation of the rare non-appearance of a phantom after amputation.

The Occurrence of Unnatural Attitudes or Abnormally Free Movements

Unnatural attitudes occurred in only a few instances, almost always in the hand. The reason sometimes came out in the history, for example, an airman with a forearm amputation had a typical phantom except that the thumb was markedly extended ; the last thing he remembers before being wounded was pressing hard with the thumb against part of the gun in an effort to get it working—the phantom thumb appeared in the same position and was at times slightly painful.

Frequently, however, there is no discoverable reason for the unusual attitude, which is usually a simple modification of the natural position and within anatomical limits, though sometimes rather forced, and they do not worry the patient to any extent, for example, when the fingers are heaped up consecutively on the index as children do. As in the case just quoted they are akin to the superadded sensations in the first group, and seem to depend upon the memory of a previous experience. In rare instances the positions are so unnatural and fantastic, as when the fingers are grossly twisted and interwoven, that they can hardly be related either to any previous experience, or to afferent impulses from the divided nerves and muscles in the stump.

Similar inexplicable behaviour was also seen a few times on the motor side. Normally, voluntary digital movements depending on the usual organic reflexes are restricted in range, consist simply of flexion-extension, and are always associated with slight contraction in the appropriate stump muscles. As an example of abnormally-free " non-organic " movements, a man with a leg amputation always asserted that he could move the phantom foot through the full range in all directions, including inversion and eversion (which we have never found to occur in a natural phantom), and that ankle movement was as easy as toe movement and just as in the normal foot, although there was no sign of concentration or effort such as is often noticeable in the facial expression. The suspicion that this was a purely psychogenically-determined phenomenon was, we considered, confirmed by the fact that the stump muscles remained motionless.

Submergence of the Natural Phantom by an Overlay of Disagreeable Manifestations

It is these cases which show the most severe disturbances but they are rare—less than 5 per cent. The usual sensory and sometimes also motor manifestations of the natural phantom are obscured in varying degree, and may be completely submerged

by an overlay of disagreeable painful sensations and gross, bizarre digital distortions beyond anatomical limits. This group includes the spasmodic, involuntary, uncontrollable, and often painful movements of the digits, which are more common after proximal amputations, occur in the absence of voluntary movements, and may disappear after a satisfactory re-amputation; the occasional irregular jerkings of the stump, usually at times of emotional upset; and sometimes, we believe, the cramp-like muscular pains in the phantom. These various manifestations are, we would suggest, psychogenically determined and, in a few patients, this suspicion was confirmed by the later development of outspoken functional symptoms.

The painful sensations often have a burning or boring quality, like raw flesh or red-hot needles or even slimy and wet, sometimes limited to the hand, but usually involving the *whole* limb without any gaps, so that there is no distinction between parts having different degrees of central representation. The pain may be intermittent but, like many psychogenic pains, is often constant and without variation either from time to time, or between different parts of the phantom. The attitude of the proximal segments is hardly ever affected, but in one exceptional case a complete phantom occupied an unnatural position in a straight line obliquely across the front of the body at an angle of 45 degrees to the line of the arm stump; it was continually painful, and, in addition, there were sometimes painful involuntary movements of the fingers, which, however, could not be moved voluntarily.

We had two or three cases showing constant burning pain in upper limb phantoms and a tender hyperæsthetic stump—a condition resembling if not identical with causalgia.

It appears that psychogenically imposed sensations are predominantly painful and never consist of the simple tingling of the natural phantom. It is also interesting to note that the sensations which may appear in a phantom seem to reflect, as regards their duration, three levels of sensory activity, namely, the psychogenic pain which is constant, the sensori-motor tingling intermittent and of intermediate duration, and the stump neuroma response which is momentary.

From a study of the foregoing groups it would seem that the mind can subconsciously impose in varying degree a great variety of sensations on to the stereotyped natural phantom. The milder manifestations represent incidents of varying psychological importance in the patient's past experience, but their appearance and severity depend upon the personality of the patient. The most extreme development is, we believe, evidence of a hysterical personality. The disturbing mental effect of uncertainty regarding pension, etc., may undoubtedly focus attention on the amputation, and we suspect that this factor is often important in civilian accident compensation cases. Assuming that psychogenic suppression of the natural phantom or imposition of overlay sensations may occur, we often wondered whether the reverse mechanism occurs and if the occasional phantoms in which there was no evidence of fading out were, in fact, for some reason being psychogenically perpetuated. One man, for example, with an unusually persistent and strong phantom had been told by the surgeon that he would feel the nerves for four years and it looked as if he would. What appeared to be a perpetuating influence, dependent on dissatisfaction, was seen in several cases requiring re-amputation, as described below.

SECONDARY STUMP OPERATIONS

In many cases secondary operations were carried out on the stump—about twenty re-amputations, more than thirty neurectomies, and many sequestrectomies—mostly from about six months to two years after amputation. Some of these men and many others had already had secondary suture of guillotine stumps, re-amputation, sequestrectomy, etc., during the earlier months, often before we saw them, without any noticeable effect on the phantom as far as could be judged from their descriptions. Observations before and after our own operations confirmed the impression that operation on the stump, whether or not the nerves are re-divided, had no effect on the phantom except in the special circumstances described below.

Re-amputations were done, (*a*) to convert an unhealed guillotine stump into a soundly healed one, usually by removing about two inches of bone and suture of flaps, and (*b*) in a few cases to remove a troublesome, useless knee or elbow. Neurectomy was performed to stop troublesome pins and needles from a superficial neuroma, usually in arm or below-knee stumps. When the nerve contained no muscular branches it was divided high up where the fresh neuroma would not be subjected to future trauma, for example, the ulnar and median nerves in an arm stump were divided in the axilla. Several inches of nerve were excised and the neuroma not removed unless the stump was being trimmed.

Neither operation, generally speaking, had any effect on the strength, telescoping or willed movements of the natural phantom. Occasionally, however, either procedure caused complete disappearance of the phantom. This seemed to happen

when the patient was particularly pleased with the result of the operation, and especially when the stump had remained troublesome after several previously unsuccessful operations, troublesome not so much from pain as from the annoyance of requiring constant dressing for one or two years, and perhaps also from recurring inflammation. The satisfaction of at last having a well healed stump and discarding the dressing seemed to suppress everything connected with the amputation, including the phantom. One man, for example, had had two unsuccessful operations in an attempt to heal a discharging stump between nine and eighteen months after amputation; the third secondary operation was successful and the phantom, previously quite strong and painful, completely disappeared. He said that he had been very disappointed with the second attempt, after which he began to experience pain in the phantom. This late appearance of pain was observed in several others when they began to realize that the stump was slow in healing and was preventing them getting an artificial leg. It was not seen in the first few months when unhealed stumps were the rule and accepted as a normal occurrence.

Suppression of the phantom was also seen after several neurectomies. The reason for this was not so apparent as after re-amputation, since the operation was done simply to abolish the pins-and-needles from a neuroma. There was, however, usually other evidence in the phantom of functional overlay or suppression, and the patient's mind, possibly unusually suggestible, was evidently ready to assume that the operation would cure "the nerves" completely. This abolition was observed for at least a year: whether it remained permanent thereafter is not known. It is important to appreciate that suppression of the phantom, even when painful, may occur after simple operations on the stump in certain cases, as well, apparently, as after tractotomy and cortical excision, but of these latter operations we have no personal experience.

The disappearance of a functional overlay sensation with the subsequent emergence of the already weakened natural phantom following a satisfactory operation is illustrated by the following case.

A man with a mid-arm stump was first seen two years after amputation. Cosmetically, the stump was bad, infection was present and there was a large redundant fold of soft tissue hanging loosely from the end. He experienced a constant unpleasant dragging sensation and feeling of weight on the end of the stump, which he said had always been present, and he could recall no other sensation. The stump was repaired by removing one or two inches of bone, and the flaps healed immediately. He was delighted with the new stump and "glad to be rid of the bandage." He then remarked that the unpleasant dragging sensation had disappeared, but, instead, there was a vague sensation of the index and thumb on the end of the stump which he had never felt before; it was a mild tingling, quite pleasant and "not disagreeable like the dragging." This was evidently the natural phantom and it was just at the expected stage for that period after amputation. It is assumed that the gradual fading of the natural phantom had been taking its usual course and it entered consciousness only after the functional overlay sensation had disappeared.

DOUBLE AMPUTATIONS

Our observations on double amputations are few and incomplete. In general, the various features of double phantoms are about the same on both sides. There are, however, usually minor differences of detail. The two phantoms may appear simultaneously or independently indicating, presumably, that their respective cerebral connexions function separately. Again, one phantom may disappear before the other; for example, we observed over a long period a man with arm and thigh amputations on the same side; the phantoms were at first typical though the hand was always stronger and was still readily perceived after the foot had disappeared at about eighteen months. It was our impression that the phantoms after symmetrical amputation were, on the whole, weaker than after the removal of one limb. Hemispheral dominance had no noticeable influence on double, or, seemingly, on single phantoms.

During the Ardennes fighting in the winter 1944–5, we saw six men with severely frostbitten feet necessitating double amputation, usually below the knee, after six or eight weeks. The amputations were done separately with an interval of ten to fourteen days, which afforded a good opportunity to get the patients to compare the sensation of the phantom foot with the dead foot. These observations supported previous conclusions about phantoms generally. The anterior halves of the feet and usually a part of the heel were black and hard from dry gangrene. The pre-amputation sensations consisted of momentary sharp pains, often caused by movement, in the demarcation zone across the foot, and, sometimes, constant pain in the heel due to pressure. The pain occasionally radiated into the toes but never appeared there alone, and there was no phantom-like tingling. It was usually intermittent and relatively mild, and unlikely, therefore, to overshadow any tingling in the dead toes had it been present.

After the first amputation, typical phantom tingling appeared in the toes, especially the great

toe, usually during quiet periods, and it remained for at least several minutes. When the tingling was stronger it also appeared in relation to the heel, instep, etc. In addition, the momentary pre-amputation pains in the foot were sometimes superadded, but they disappeared within two or three weeks, leaving the patient more conscious of the phantom toes. Tingling also appeared if only the toe was removed by completing the line of demarcation at its base, which meant dividing only the last bit of dead joint-capsule and flexor tendon. The difference between the pains in the gangrenous foot and the tingling in the phantom toes was easily appreciated ; they appeared at different times, the one in response to movement and the other when quiet. After the second amputation, the two phantoms appeared either together or separately, and they were not necessarily identical in strength (the second was the stronger and sometimes the only one to appear) or in distribution (depending on pre-amputation sensations).

As regards the micturition effect, there was no definite instance of it occurring before amputation, but it always appeared afterwards, usually as a tingling on the end of the stump, which was sometimes preceded by a shivering sensation which ran down from the thigh. After the second amputation the sensation always occurred simultaneously in both legs and was usually similar in strength, though sometimes it was stronger on the more recently amputated side ; its strength, therefore, seemed to depend on the responsiveness of the related central connexions, as the stimulus from the bladder was the same for both. During the first few weeks, the micturition effect was often stronger than the spontaneous phantom and was sometimes the only sensation to appear, but it rapidly faded and soon was hardly noticeable.

Voluntary movement of the phantom toes was not possible for a month or two and at first was often unilateral, appearing first in the earlier amputated leg, when toe movement induced tingling on that side but not the other.

Multiple phantoms can thus appear independently or, in certain circumstances, simultaneously though modified by local features such as the age of the phantom. Further study of double and especially asymmetrical amputations might yield much interesting information.

MINOR AMPUTATIONS

Partial removal of a hand or foot or even part of a digit, is followed by the appearance of a phantom which is essentially the same as after major amputations. It is, however, less noticeable, possibly because the absence of a digit causes little inconvenience, and mild tingling in a finger when the rest of the hand is normal is not so strange as when the whole arm is missing. Nevertheless, digital tingling is not much weaker after simple removal of a digit than after amputation of the whole limb, and it has the same quality. Any slight difference in strength is thus disproportionate to the size of the missing parts. In general, the strength of any phantom may be said to depend on the vividness of its terminal phalanges ; it does not seem to matter how much more of the limb is removed, for that often results merely in the appearance of additional, and usually weaker, parts which, as it were, support the digits.

When several fingers are removed individually, there is the same difference in the strength and persistence of their several phantoms as after a major amputation, so that all may be felt during the first year or two, but the thumb and index are stronger than the others (the latter appear only during the winter), and they persist for a year or two longer. The toes are considerably weaker ; the great toe rarely lasts longer than a year or two, and the lesser toes may never appear.

The three main features of major phantoms may also occur after minor ones, namely, the spontaneous natural tingling, the pins and needles from a digital neuroma, and, very rarely, constant pain or other disagreeable features, probably of psychogenic origin. Minor phantoms are, however, generally mild and rarely troublesome. Phantoms after minor amputations, then, are minor only in the sense that a small part has been removed and not as regards their strength, in which respect they are similar to larger phantoms.

DISCUSSION

This study of limb phantoms has shown that a phantom is a natural and almost constant sequel to amputation, and not, in fact, a pathological manifestation. Fundamentally, it is a stereotyped though complex phenomenon. Occasionally, additional features introduce such marked variations that before seeking a general comprehensive explanation for the phantom it is advisable to analyse the various sensations which may occur and the conditions under which they appear. The more general, almost universal, properties may be considered first, and then the epiphenomena which are peculiar to the individual.

We found the great majority of phantoms were painless. When, for instance, ninety-eight men in one batch were questioned at periods up to six

months after amputation in 1940, only four complained of " the nerves." This incidence of pain is much lower than is often supposed and, indeed, our series gives a different general impression of phantoms from that described by other writers due, perhaps, to the distinctive type and age-group of our patients. Lhermitte (1939) found only three instances of painful phantom in his thirty cases, but implies that this is much lower than the commonly supposed incidence, whereas Riddoch (1941) states that nearly half are painful. However, it may be that pain is more common in phantoms after amputation for trauma or in older people with arteriosclerosis, just as post-herpetic neuralgia and other pains are more distressing in later years.

It was soon realized that, while conspicuous disagreeable features were rare, for not more than two per cent. of patients complained seriously of pain, the more pleasant tingling, which almost always appeared, constituted the fundamentally important part of the phantom. Its constancy and uniformity strongly suggested an organic basis, with allowance being made for individual variation in obtrusiveness and strength, reflecting, no doubt, normal differences in the degree of cerebral activity. The motor manifestations were thought to be even more characteristically organic because of the objective evidence of sensori-motor reflex activity in the associated muscle contractions. It is important to recognize their close relationship and to distinguish them clearly from other more incidental features. We refer to these basic phenomena as the " natural phantom." It is characteristically mild and patients quickly get used to it so that it is rarely, if ever, a cause for complaint and never requires treatment.

All who have studied phantom limbs have naturally been concerned with determining the physiological level in the nervous system to which the existence of the phantom is to be attributed. We feel no obligation to combat the view, once widely held, that it is a purely hysterical manifestation, but we wish to point out that the features which distinguish the phantom from frankly psychotic hallucinations are found in that component which has been designated the natural phantom.

The manifestations of the natural phantom have been sufficiently described and the speculations to which they give rise already referred to. Here it is only necessary to stress the constancy of its appearance, the stereotyped form which it assumes, and especially the fact that the most vividly perceived and enduring parts are precisely those with the greatest cortical representation. We believe that its anatomical substrate is in the sensori-motor cortex.

The tingling is a positive sensation which presumably reflects increased activity in the sensory cortex. Its behaviour and relation to the factors which influence it suggest that it is more likely to originate spontaneously in the cells of the cortex than to be secondary to afferent impulses from the divided nerves in the stump. The main reasons for regarding it as a cerebral rather than a peripheral nerve phenomenon are: (1) The distribution of sensory tingling and of voluntary movement correspond with the extent of their respective cortical representation, and not to the anatomical distribution of a peripheral nerve. (2) The close functional correlation between sensation and willed movement. (3) The factors which intensify or induce the phantom arise from all levels of nervous activity. There is no evidence that the natural phantom is influenced by mechanical stimulation of the divided nerves, though the sensation thereby induced is correctly orientated. Were the tingling peripheral in origin and due to stimulation of the sensory cortex by constant mild impulses from the stump (and it may be), it could hardly be induced by central reflexes unless the cortex were in a state of heightened activity. Strong pain impulses from a traumatized stump submerge the phantom, just as happens when cerebral activity is diverted in other ways. (4) The phenomenon of telescoping, though not explained, is at least comprehensible if regarded as an expression of the slowly progressive obliteration of parts according to their cortical representation. Telescoping is a main argument in support of a cortical basis for the phantom, for it is perhaps the most complicated phenomenon and could hardly result from changes at a lower level. It reveals the integration of all influences that enter into the phantom-complex from those psychogenically determined at the highest levels to the simplest organic stimulus from a stump neuroma, and, as it were, fits them in to the final common path—the size and shape of the phantom. (5) As already indicated, it is among the varied phenomena of willed movements, rather than the sensory impressions, that the most suggestive evidence of cortical activity is found, and insufficient attention has been given to this feature in the past.

It seems as if immediately after amputation the related sensory cortex is temporarily in a state of increased activity which, however, gradually decreases during the following months. At first this activity is so strong that the phantom appears spontaneously in consciousness, whereas positive appreciation of a normal limb occurs only when a stimulus is received from the periphery. The related cortical field is, as it were, in a more receptive state than the remainder of the cerebral cortex and

can respond to a variety of nervous impulses. Later, as the hyperexcitability subsides, the tingling ceases to appear spontaneously in consciousness, but still does so in response to reflex stimulation. Finally, the stronger inducing agents, or even direct stimulation of sensory fibres in the stump, fail to evoke any conscious sensation of the amputated part. Recently we observed, in a different connexion, a case which illustrates this final stage.

The patient was a woman from whom one of us removed a spinal neurofibroma attached to the seventh cervical root. Twelve years previously the index finger had been amputated at the proximal interphalangeal joint, following which she noticed the phantom tingling for the next two or three years but not afterwards. During recent weeks the neuroma had produced pins and needles in the thumb, middle, and ring fingers, but no sensation whatever was referred to the index. Transient, more severe post-operative pains had the same distribution. It may be assumed that the fibres from the stump of the index were stimulated in the root, as were those from the neighbouring digits, and it is interesting that the sensory cortex subserving the index finger, at first more active than the rest, eventually ceased to respond to stimuli from its afferent field.

Variability of cortical excitability and its eventual disappearance lead to the subject of subconscious cerebral activity. Although the phantom is essentially a conscious phenomenon, we have frequently referred to features which may be regarded as evidence of nervous activity at a subconscious level. For example, the gaps in an untelescoped phantom, which yet behaves as if it were complete, must still be represented centrally although not consciously perceived ; for otherwise, in the late stages of a distal amputation, it would not be possible to move the digits (which requires sensory guidance) if they were not still represented subconsciously. This, presumably, merely reflects normal subconscious cerebral activity. As the phantom weakens the decline of cerebral activity, shown at first by the cessation of conscious tingling, seems to go further, and in time the subconscious activity also fades out, as indicated by the disappearance of the gaps and of voluntary movements. We have thus been led to think, though not without hesitation, of activity at conscious and subconscious levels, and to regard the phantom as having truly disappeared only after the extinction of the latter phase. Only thus can we explain the difference between mere absence of positive sensation in a gap and the subsequent disappearance of the gap in the telescoped phantom.

The threshold of cortical excitability, being a functional and not an anatomical affair, is not uniform for the whole limb but is related to the relative degree of central representation of its parts. Increased excitability in relation to the fingers may persist after total disappearance of even subconscious representation of the weaker segments, giving the impression of a " baby arm with a large hand " and eventually of complete telescoping. One interesting feature of telescoping is that a segment, or any part of a limb, does not suddenly disappear but decreases in size gradually and evenly, a process which perhaps gives an inkling of the extremely complex neuronal process involved.

Our observations appear to indicate that the functional changes in the brain (and possibly also spinal cord) following amputation are limited to the centres associated with the missing part, except, it would seem, for a slight secondary involvement of centres for neighbouring structures in the stump (increased tone, sweating). These fields of altered excitability or function are affected differently by the various phantom-inducing stimuli according to their origin, for example, the effect of willed movement does not spread to another phantom, whereas micturition affects both of lower limb phantoms, but not upper, while a severe stimulus like the shock of falling affects any phantom. It seems there is no widespread disturbance of cerebral activity although its general intensity appears to influence the strength and possibly the rate of disappearance of the phantom and therefore perhaps may account for individual variation in these properties.

There can be little doubt that the central neuronic connexions subserving sensory and motor functions between different parts of a limb continue to maintain their functions after amputation, both within the phantom and between it and the stump. Those who have stressed the importance of peripheral irritation in generating the phantom point out that the phantom follows the moving stump. This movement of the phantom, however, depends simply on the interpretation of proprioceptive impulses arising in the muscles of the stump. In fact, it supports the hypothesis of the central theory, for it shows that afferent impulses from the parts yet remaining (the stump muscles) are still in functional relationship with that part of the cortex in which resides the substrate of a consciously perceived gap between the phantom digits and the stump. To put the matter briefly, that which still exists is working in harmony with that which has ceased to exist *except as a pattern in the cortex*.

The analysis of central neuronic connexions may be pushed to a more speculative stage concerning activity at conscious and subconscious levels. It is easy to conceive that during stump movements when there is little or no gap in the phantom (as

after wrist disarticulation), the muscle afferents can maintain their neuronic connexions with the centres for the distal part of the phantom so that the stump and phantom move as a whole, for this is merely the normal proprioceptive mechanism when moving a rigidly held limb at a proximal joint. When there is a large gap in the phantom, including intervening joints, as between digits and shoulder, this connexion is still maintained, again, at a subconscious level, as in the normal limb. Later, when the subconscious gap has disappeared, functional connexion still remains between the stump muscles and the fully telescoped digits.

The continued harmony between centres is intimately bound up with the shape and size of the phantom and with telescoping. The original connexion between the digits and the stump may be by a long direct pathway or by short intersegmented relays. In either case the final link, after the intervening parts have faded out, is presumably direct. The digits, the leading part of the limb, thus continue to work with the stump, or perhaps with the girdle muscles, after the subsidiary supporting segments have disappeared.

This brings us to the extraordinary and probably very important phenomenon of the final inclusion of stronger digits within the normal anatomy of the stump, in which they may still be identified and moved voluntarily. This may also occur momentarily when the stump touches a solid object. The reference to the stump of the sensation aroused by stimulating a neuroma, and the sensation which runs down the stump during micturition, swallowing, etc., are probably of a similar nature. These represent a kind of extended final stage of telescoping and may be related to the mechanism known to neuro-physiologists as deviation of response. It may be that the cortex associated with the normal stump structures takes over the function of the abnormal digital cortex. Even more direct evidence pointing in the same direction is the transfer, after the phantom has disappeared, of the sensation on stimulating digital sensory fibres in a neuroma (which remain sensitive) to the normal skin of the stump.

We have assumed that the phantom is essentially a central phenomenon and have stated what seems to happen in terms of change in excitability and threshold differences, but we are still ignorant of the actual physiological processes involved or of their ultimate significance. The only obvious effect of amputation is division of the nerves, and if it is assumed that the phantom does not result from persistent irritation of nerve ends it follows that we must look for the cause in the isolation of central mechanisms from their natural peripheral connexion.

The phantom shows evidence of nervous activity at all levels. On the motor side can be seen the effect of the normal decreasing voluntary control of limb muscles from the most voluntary in the distal part to the most automatic at the proximal ; while the sensory component shows evidence of the lability of the cortex, a subject recently discussed by Walshe (1943). Lability of the cortex is further suggested by the final inclusion of the digits inside the stump, and even more directly by the transfer after the phantom has disappeared, of the sensation on stimulating digital sensory fibres to the normal skin on the stump.

The foregoing remarks suggest that the natural phantom depends upon changes in the spontaneous activity or threshold in the cortex following the loss of those impulses it normally receives from the amputated part. The " sensation " (or the absence of a conscious sensation) of a normal limb (for instance, a hand) quite likely depends upon the balanced integration of a multitude of impulses of all kinds constantly coming from many sources including the part of the limb representing the stump (for example, concerning weight and balance). It may be that the conscious appreciation of phantom tingling results (to adopt a suggestion made by Walshe (1942) in relation to other forms of disturbed nervous function) from the centres becoming unbalanced by the absence of normally opposing activities, or by liberation from a controlling influence (which would be from the missing part). We think that disturbance in the normal interaction between impulses from distal and proximal parts of the limb is important, and it may be that girdle structures are necessary for deviation of response. There is no evidence that the change goes beyond the limb, and the complete absence of impulses from a limb after spinal transection may account for the absence of a phantom in spinal lesions.

On the motor side, not only are the main movements of the hand consciously appreciated, but also the weaker secondary and tertiary contraction in proximal muscles. It is likely, however, that the contractions of the latter muscles (which are unmasked after amputation) occur normally during purposive movements of the limb though they are obscured by the more obvious contraction of the stronger supporting postural muscles.

The increased tone in the stump muscles evidently results from increased central excitability and is reminiscent of a release phenomenon. The leading part of the limb is an organ of movement and exploration acting under a high degree of voluntary direction which controls in some degree the contractions and possibly the tone of the more proximal

supporting muscles. It is thus perhaps permissible to assume that when this control from the digital area is lost, as after amputation, the tone in proximal muscle groups is necessarily altered. Though this alteration in tone is the result of stimulation from the disturbed and hyperactive cortical areas, it appears to be a release from peripheral control rather than from higher centres as occurs in pyramidal lesions. The later diminution in cortical excitability would account for the ultimate reversion to more normal tone.

If it is assumed that the phantom reflects mechanisms in cerebral physiology then the motor manifestations show clearly a number of interesting features which have been described already and need only be recapitulated : (1) the close association between the motor and sensory cortex, which in fact function as one, and the primary importance of sensation in initiating voluntary movement ; (2) the distinction between the more voluntary and the less voluntary movements in relation to their sensory control and the different types of muscle fibres concerned ; (3) an interesting motor mechanism which can activate the stump muscles in the absence of sensory guidance without, however, initiating movements in the phantom.

It has been seen that the only movements of which the phantom fingers are capable are flexion and to a lesser degree extension. If the central neuronic processes subserving more individual digit movement are intact, why, it may be asked, is the patient unable to perform such highly voluntary movements as abduction and adduction of the digits. Some insight into this anomaly is afforded from the fact that though such movements are highly voluntary, they are quantitatively weak by comparison with general finger flexion. In this connexion it may be noted that finger movements on cortical stimulation (Penfield and Boldrey, 1937) are limited to flexion and extension, and this too is what is seen clinically in epileptic movements.

There are, however, difficulties in accepting denervation, important though it appears, as the sole cause of the changes in the cortex. For example, we have not encountered a phantom in denervated digits after peripheral nerve injuries, in spinal lesions, or in gangrene. It may be that in these circumstances a phantom would be in conflict with sensations arriving at the cortex, not from the digits, but about them. It is, for example, possible that the slightest impression of weight from the insensitive part by pulling through tendons, joint capsules, etc., even though they are dead as in frost-bite, is enough to inform the cortex of the true state of affairs. An example of such inhibition of a phantom mechanism, on the motor side, by extraneous normal sensations with which it would be in conflict, is seen in the absence of toe movement and twitching of thigh muscles when a below-knee stump is completely denervated.

We have never encountered a true phantom after peripheral nerve injuries, such as complete lesions of the sciatic nerve with denervation of the toes and forefoot, or of the brachial plexus with an insensitive hand. It is just possible, though unlikely, that some impulses are conveyed from these somatically-denervated areas by sympathetic fibres accompanying the blood vessels. Patients with complete plexus lesion may say they occasionally feel the fingers, but this seems to be the momentary pins and needles due to stimulation of a neuroma and is, in reality, Tinel's sign. The digits to which this sensation is referred never show the phenomenon of telescoping. We were never satisfied that true phantom tingling appeared in totally denervated digits which, so far as their intrinsic nerve supply is concerned, might just as well have been amputated.

It would seem from the behaviour of phantoms that the knowledge that a limb is missing has little or no importance in their genesis. Conversely, it is unlikely that the known presence of an insensitive part would prevent the appearance of phantom-like sensations in relation to it. The only apparent explanation is that the presumed tendency for the cerebral cortex automatically to enter a phase of heightened activity in the absence of afferent stimuli from the denervated part is inhibited by information from the remainder of the limb. Such information would indicate the continued presence of the insensitive part : there might, for example, be no alteration in weight or balance or in the tension of undivided long digital muscles.

True limb phantoms do not seem to occur after complete spinal lesions, although over-anxious patients sometimes assert that they can feel the toes. We have had no opportunity to observe the effect of a permanent spinal lesion or of spinal anæsthesia on lower limb phantoms. When the limbs are normal, spinal anæsthesia produces a transitory tingling as sensation is disappearing which is apparently similar to that in phantoms, but, as the anæsthesia becomes complete, the tingling disappears and is replaced by a feeling of heaviness of the legs. It thus appears that simple isolation of a limb from the sensori-motor cortex cannot alone generate a phantom and that an additional factor is necessary, coming either from the girdle structures at the base of the limb (disturbance of balance, etc.) or from the ends of the divided nerves. We saw recently a man with double thigh amputation in whom an inflammatory lesion in the upper dorsal spine, producing complete motor and sensory loss

below the level, abolished the sensation of the phantom toes and the ability to move them. A few weeks later, however, as the lesion gradually subsided, the phantoms returned along with recovery of sensation on the trunk and movement of the stumps.

In regard to the occasional accompaniments which have already been discussed and illustrated, we have come to regard them as a reflection of individual peculiarity and not as an essential part of the phantom, for they represent (*a*) a psychologically-important experience in a normal person, (*b*) an outlet for a psychopathic personality, or (*c*) a fixation object for a compensation neurosis. The more we saw of these manifestations, the more impressed we became with their similarity to hysteria, and it was interesting to see how the organic features of the natural phantom might be suppressed, as in hysterical anæsthesia or paralysis, or perverted into pain or involuntary movements. When one considers the complex and highly organized nature of many of these sensations, it becomes evident that they cannot result from stimulation of divided nerve fibres ; there seems, in fact, to be no alternative to the supposition that they originate at a high level in the nervous system.

We believe that the phantom portrays normal *physiological mechanisms in the nervous system*, and may, in fact, provide an avenue for their study. This belief in the organic behaviour of the natural phantom is strengthened by observations and conclusions made in totally different circumstances, namely : (1) the clinical phenomena of motor convulsions in epilepsy so analytically studied by Hughlings Jackson (1931), who pointed out the varying degree of voluntary control of different muscle groups, and the cortical representation of movements rather than of muscles ; (2) the work of Penfield and Boldrey (1937) on cortical stimulation in man, especially as regards representation in the sensory cortex ; (3) the primary importance of sensation in initiating movements shown by Mott and Sherrington (1895) in the deafferented monkey's limb, an experiment which had the effect of abolishing movements of the distal part of the limb while those depending on the proximal (less voluntary) muscles were much less impaired.

In peripheral nerve injuries we have been impressed, in cases with partial recovery, by the exactly similar distribution of grades of recovery, both sensory and motor, to that of the tingling and movement in phantoms, though it is, of course, reversed. This agrees with the accepted view that the final stages of complete recovery after nerve injuries depend on cortical integration, which, in turn, requires perfect peripheral regeneration. When this is lacking, as in partial recovery, the more highly represented distal muscular and sensory functions lag far behind those of the more proximal structures.

In *treatment* it must first be decided to which group of symptoms (natural phantom, neuroma irritation, causalgia, or mental accompaniments) the patient's complaints belong, for they are sometimes interwoven and require careful analysis. In cases with severe mental manifestations an attempt should be made to discover the underlying cause, such as domestic worry (which precipitated the symptoms in several of our cases), unsettled compensation, or occasionally a latent psychosis. It is unnecessary to attempt altering the course of the natural tingling, about which the patient may complain in the early weeks during the initial disappointment of unexpectedly losing the limb. Knowing that this part of the phantom subsides sufficiently to be unnoticed after, say, six to eighteen months, the patient should, if necessary, be told it will weaken in the course of months, without, however, fixing any time limit.

We have no experience of attempting to relieve the more serious painful manifestation by spinal, cerebral, or sympathetic operations, though good results have been reported by others. It was found, however, that some patients are in such an impressionable state after past disappointments following inadequate operations, that even a peripheral operation, if satisfactory, is followed by complete suppression of the whole phantom. Such disappearance of symptoms, which may affect both natural phantom and overlay manifestations, can hardly depend on any " organic " change and must make us cautious in assessing the results of central operations.

SUMMARY

1. A study of some three hundred cases of amputation showed that a phantom limb is a natural and almost universal sequel to amputation.

2. Three kinds of sensory phenomena may appear ; (*a*) mild tingling, which forms the basic part of the phantom in nearly every case and probably arises in the cerebral cortex ; (*b*) stronger pins and needles induced momentarily by touching a neuroma in the stump ; (*c*) occasionally, superadded sensations which may be disagreeable and painful and probably have a psychogenic basis. Rarely, a syndrome resembling causalgia is seen.

3. Special attention has been given to what is termed the " natural phantom " by which is meant the basic sensory tingling, its motor counterpart, the impression of willed movements, and other

features. The spontaneous tingling appears in those parts (chiefly thumb, index, and great toe) having the largest cortical representation, and the belief that it originates in the sensori-motor cortex is strengthened by its close functional relationship with the motor phenomena. The willed movements also are stereotyped, and are most developed in relation to leading parts of the limb; they are associated with observable contraction of the appropriate muscles in the stump, and their behaviour reflects the fundamental importance of sensation in initiating and controlling voluntary movements. The phantom can be induced and intensified by a variety of reflex factors (for example, micturition) acting centrally.

4. The behaviour and evolution of the "natural phantom" is as if the related cerebral centres were for a time in a state of heightened activity, the later subsidence of which results in telescoping of the phantom and its eventual fading from consciousness, and perhaps also in the disappearance from subconscious levels of its neuronal patterns.

5. Unusual superadded sensations sometimes appear which are peculiar to the patient, and are believed to be psychogenically determined from the highest cerebral level. They may be mild, representing incidents in the patient's past experience, or, rarely, disagreeable—severe spontaneous pain, distorted attitudes, and involuntary spasmodic movements—dominating the phantom. The continuation in the phantom of pre-amputation pain or posture seems to be determined, in many cases at least, by its psychological importance and not by its severity or duration.

6. The phantom cannot, therefore, be considered as a single entity for its manifestations may be derived from three levels in the nervous system (psychogenic, sensori-motor cortex, and peripheral nerve), and, before operating, it is important to determine to which of these the patient's complaints are most attributable.

7. Peripheral operations on the stump, apart from neurectomy for a sensitive neuroma, usually have no effect on the phantom. Occasionally in suggestible patients and following a gratifying operation on the stump the phantom may be suppressed.

References

Denny-Brown, D. E. (1929). *Proc. roy. Soc. B*, **104**, 371.
Hughlings Jackson, J. (1931). "Selected Writings." Edited by J. Taylor, and others. London.
Lhermitte, J. (1939). "L'image de notre corps." Paris.
Mott, F. W., and Sherrington, C. S. (1895). *Proc. roy. Soc.*, **57**, 481.
Penfield, W., and Boldrey, E. (1937). *Brain*, **60**, 389.
Riddoch, G. (1941). *Ibid.*, **64**, 197.
Walshe, F. M. R. (1942). *Ibid.*, **65**, 48.
——(1943). *Ibid.*, **66**, 104.

PAIN SENSIBILITY IN DEEP SOMATIC STRUCTURES

BY

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Introduction

It is well recognized that pain may be provoked by the stimulation of many deep-lying somatic structures, such as muscle, tendon, periosteum, etc. (Lewis, 1942). It was noted by Lewis (1938) that the quality of this pain is independent of the method of stimulation adopted, and that it differs markedly from the quality of the pain which can be aroused from skin. In consequence he suggested that the pain nerves of the skin form a system different from that to which those nerves supplying deeper tissues belong. This contention he supported by observing that the reflexes resulting from painful stimulation of the skin and those due to stimulation of deep-lying tissues tended to be of a different character. In 1939, Lewis and Kellgren brought forward additional evidence for the specificity of reflex responses obtained from these two sources. So far, however, no anatomical evidence has been produced which would lend colour to the theory of two separate systems subserving the sensation of somatic pain.

It has been shown (Weddell, 1945) that in normal skin the network of nerve endings subserving the sensation of pain is disposed in such a manner that any one area of skin is supplied by several overlapping terminals derived from different axons. Weddell, Sinclair, and Feindel (1948) have recently investigated the innervation pattern of skin from which an abnormal reaction to painful stimuli was obtained. They found that in such areas the terminals associated with painful sensation were invariably isolated from each other, and that the interweaving of adjacent terminal fibres which is characteristic of the normal skin did not occur. As a result of this investigation they suggested that alterations in the peripheral pattern of innervation of the skin may be responsible for alterations in the quality of the sensation perceived following the application of a painful stimulus. Thus they explained the occurrence of "protopathic" pain in many clinical conditions affecting the peripheral sensory nerves.

From this work it appeared that the difference in quality observed by Lewis (1938) between "skin pain" and "deep somatic pain" might be due to differences between the pattern of innervation in skin and in deeper tissues. Accordingly, it was decided to make an investigation of the innervation patterns in representative deep-lying tissues, and to compare them with the innervation pattern of the skin.

Observations

Rabbits were perfused with methylene blue solution according to the intravenous drip technique described by Feindel, Sinclair, and Weddell (1947), which allows of the examination of neural patterns in whole tissues. By this means a study was made of the main features of the innervation of skeletal muscle, deep fascia, and periosteum from different regions of the body.

It was found that there is considerable variation between different pieces of the same tissue, more especially when the pieces are derived from different parts of the body. Nevertheless, the main features of the innervation pattern in the three tissues are clearly distinguishable.

(*a*) *Muscle.*—In addition to the complex network of motor innervation and the complement of nerve fibres supplying the muscle spindles, all the muscles examined contain a number of fine beaded fibres, which run either in connective tissue septa within the muscle, or as "accessory" fibres to muscle spindles. The general pattern formed by these fine beaded terminals has two main characteristics. The first of these is that these terminals form a very loose meshwork, with relatively large gaps where no fibres or endings are to be found, and the second is that the individual neural terminals in this meshwork are invariably isolated from each other (Figs.

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1 and 2). There is thus no interweaving between adjacent terminal fibres such as occurs in the case of similar fibres in the skin (Fig. 7), nor does superimposition of the territory of one fibre upon that of another occur.

(*b*) *Fascia.*—In the portions of deep fascia studied, a similar but rather more dense network of fine beaded fibres occurs; this network is, however, much less closely woven than that characteristic of the innervation of the skin. Though individual fibres are generally isolated from their neighbours (Fig. 3), in a few cases a certain amount of interweaving takes place (Fig. 4), and the territories of such interweaving fibres may overlap each other.

(*c*) *Periosteum.*—In the portions studied, the meshwork of beaded fibres tends to be more dense than in either muscle or fascia. Interweaving and superimposition of adjacent terminals is relatively common in these preparations (Figs. 5 and 6), but is still infrequent when compared with conditions in the skin.

Discussion

In each of the three tissues studied a network of fine beaded fibres has been demonstrated, the density and complexity of which are more evident in periosteum than in muscle, fascia being intermediate in this respect. Such networks have been observed by Hinsey (1927), Denny-Brown (1928) and Weddell and others (1940) in skeletal muscle, and by Weddell and Harpman (1940) in the case of deep fascia, tendon, and periosteum. The fibres composing the networks are exactly similar to those which have been shown to mediate nociceptive responses in the skin of the rabbit's ear (Woollard, Weddell, and Harpman, 1940). These observers showed that terminals of this type persisted in the skin after sympathectomy, and that they occurred in situations remote from blood vessels. Weddell (1941) reported that in a patient with a sciatic nerve injury an area of skin from which pain only could be elicited was examined histologically and found to contain only fine beaded fibres of this type. It is also perhaps worth remarking that the main, if not the only, sensation which can be elicited from the centre of the cornea is one of pain, and that the innervation of this region is largely composed of fine beaded fibres (Feindel, Sinclair, and Weddell, 1947). It is therefore legitimate to assume that neural networks similar to those described in the present paper are responsible for both nociceptive responses in animals and sensations of pain in man.

It cannot, however, be regarded as established that all the fibres composing these networks are capable of conveying nociceptive impulses, and many of those which run close to blood vessels may in reality be vasomotor fibres. Nevertheless, mere proximity to a blood vessel does not necessarily imply vasomotor function, since Hinsey (1927) and Denny-Brown (1928) showed that after sympathectomy a number of fine non-medullated fibres persist in relation to the blood vessels in skeletal muscle. Woollard, Weddell, and Harpman (1940) obtained similar results in the skin of the rabbit's ear, and were able to show that these remaining fibres are capable of mediating nociceptive responses.

Inman and Saunders (1944) injected irritant solutions into various deep somatic structures in volunteers, and give a list of tissues in the order of their sensitivity to this procedure. They note that periosteum is the most sensitive, followed by ligaments, fibrous joint capsules, tendons, fascia, and skeletal muscle. These observations could readily be explained on the basis of differences in the density of innervation of the tissues concerned. It should be noted, however, that while the histological evidence obtained in the present investigation is in conformity with the generalization of Inman and Saunders, sufficient variation was observed among the different tissues studied to render it likely that a broad statement of this kind might occasionally have to be qualified in order to cover comparisons between individual regions of the body. It is, however, well known to everyone who has given a number of intramuscular injections that quite large needles may often be inserted into muscle without causing any pain (Lewis, 1942), whereas periosteum is notoriously sensitive to such stimulation.* On the other hand, a painful response is readily provoked if an irritant is injected into muscle. Kellgren (1938) found that 0·3 c.cm. of methylene blue solution injected into muscle stains a volume of some 6 c.cm. of tissue, and it is therefore clear that the injection of irritant substances provides a diffuse stimulus which is more efficacious than a punctate stimulus in affecting a loose network of nerve terminals such as occurs in muscle.

Kellgren (1938) notes that pain aroused from fascia and from tendon sheaths is moderately well localized, whereas that from muscle is not. This observation also can be explained by differences in the density of innervation (Weddell, 1945), as can the relatively accurate localization of pain aroused from periosteum (Lewis, 1938; Kellgren, 1939; Weddell and Harpman, 1940). It is maintained by Kellgren (1939) that the capacity to localize pain does not depend primarily on the nature of the tissue stimulated, but is a function of its depth from the surface of the body. The experiments on which

* H. G. Wells (1896) describes a rather more drastic experiment to demonstrate the relative freedom of muscle from nerves capable of transmitting pain.

this view is founded were carried out with little regard for the local anatomy of the part stimulated, and it seems much more likely that the explanation lies in the differences in the density of innervation of the tissues concerned.

It has been noted that the intimate innervation of the tissues studied differs not only in density but also in pattern from that of the skin. In muscle, the individual nerve terminals are isolated from each other—an arrangement which is only met with in the skin under pathological conditions such as occur in certain scars, and in the territory of regenerating nerves. A painful stimulus applied to such an area of skin may give rise to pain of unpleasant quality, which is imperfectly localized and is often associated with reflex phenomena such as uncontrollable withdrawal, sweating, and dilatation of the pupil, which the same stimulus does not produce when applied to normal skin. Weddell, Sinclair, and Feindel (1948) have attributed this reaction to a reduction in the pattern of impulses reaching the central nervous system as a result of the isolation of the nerve terminals, and this hypothesis has been shown to provide an adequate explanation in many types of clinical disorder associated with an unpleasant affective reaction to painful stimuli. It may also be noted here that pain which has many of the characteristics of deep somatic pain can be elicited from the skin of a limb in which the circulation has been arrested for some time by means of a compression cuff (Weddell, Sinclair, and Feindel).

There is thus no difficulty in supposing that the " disagreeable " quality characteristic of pain aroused from deep somatic structures (Lewis, 1938) might be due merely to the observed differences between the pattern of innervation in the deep structures and in the skin.

Lewis (1938) made a distinction between the quality of pain aroused from muscle and that resulting from the stimulation of tendon, periosteum, or the web of a finger, but, owing to the difficulty with which this distinction could be recognized, it was subsequently discarded (Lewis and Kellgren, 1939). Weddell and Harpman (1940) noted that they were able to arouse pain of two main varieties from deep fascia and periosteum, one of these being similar to the " first pain " (Lewis, 1942) resulting from a pin-prick on the skin, and the other being unpleasant, diffuse, and of slower development. It is interesting to correlate these observations with the finding that in these tissues a proportion of the network of beaded fibres has the same general features as the network occurring in normal skin, and might therefore be responsible for the occurrence of " first pain." The remainder of the network, consisting of isolated terminals, might give rise to pain of the " disagreeable " quality described by Lewis (1938). It is curious, however, that Weddell and Harpman (1940) found that from tendon substance only one type of pain could be elicited—the sharp pricking pain corresponding to " first pain." This circumstance is perhaps to be explained by the fact that the observations were made on the tendo Achillis, which has a peculiarly intimate relationship to the cutaneous nerve fibres supplying the skin overlying it ; it is possible that these fibres were not adequately anæsthetized. Lewis (1942), on the other hand, notes that pain aroused by irritant injections into tendon substance is of the characteristic quality associated with deep somatic pain.

Lastly, it may be noted that the distinctions which Lewis (1938) and Lewis and Kellgren (1939) make between the reflexes aroused from deep and superficial somatic structures by painful stimulation do not appear to be of a fundamental nature. Such differences as occur may be easily explained, since the pattern of impulses reaching the central nervous system must be different in the two cases, and it is not only possible, but likely, that such different patterns should be capable of giving rise to different reflex responses.

In short, it appears that the observed differences between pain produced from the skin and that due to the stimulation of deep somatic structures can be satisfactorily explained without the necessity of postulating the existence of two separate pain-conducting systems of nerves.

Summary and Conclusions

The hypothesis of Lewis (1938) that the skin and the deeper somatic tissues are supplied by two separate systems of pain nerves has been examined in the light of the recent work of Weddell, Sinclair, and Feindel (1948), who found that alterations in the quality of pain sensibility can be produced by alterations in the pattern of the pain-producing impulses reaching the central nervous system. A preliminary examination of the innervation of certain deep somatic structures has been made, and it has been found that this innervation differs both in pattern and in density from that of the skin. These findings are sufficient to explain the observed differences in the subjective and objective results of painful stimulation of the skin and of deeper lying structures respectively. There is thus no need to postulate two separate pain-conducting systems supplying somatic tissues.

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REFERENCES

Denny-Brown, D. (1928). "On the Essential Mechanism of Mammalian Posture." Oxford University D.Phil. Thesis.

Feindel, W. H., Sinclair, D. C., and Weddell, G. (1947). *Brain*, **70**, 495.

Hinsey, J. C. (1927). *J. comp. Neurol.*, **44**, 87.

Inman, V. T., and Saunders, J. B. de C. M. (1944). *J. nerv. ment. Dis.*, **99**, 660.

Kellgren, J. H. (1938). *Clin. Sci.*, **3**, 175.

——(1939). *Ibid.*, **4**, 35.

Lewis, T. (1938). *Brit. med. J.*, **1**, 321.

——(1942). "Pain." New York. Macmillan.

Lewis, T., and Kellgren, J. H. (1939). *Clin. Sci.*, **4**, 47.

Weddell, G. (1941). *J. Anat., Lond.*, **75**, 346.

——(1945). *Brit. med. Bull.*, **3**, 167.

——, and Harpman, J. A. (1940). *J. Neurol. Psychiat.*, **3**, 319.

——, Sinclair, D. C., and Feindel, W. H. (1948). *J. Neurophysiol.* (In the Press.)

——, Harpman, J. A., Lambley, D. G., and Young, L. (1940). *J. Anat., Lond.*, **74**, 255.

Wells, H. G. (1896). "The Island of Dr. Moreau." London. Heinemann.

Woollard, H. H., Weddell, G., and Harpman, J. A. (1940). *J. Anat., Lond.*, **74**, 413.

Legends to Illustration

FIGS. 1 to 6 are from methylene blue preparations in the rabbit.

FIG. 1.—Fine beaded nerve fibre related to a muscle spindle in a lumbrical muscle. Note the absence of interweaving and the isolation of the fibre (cf. Fig. 7). A motor end-plate is seen in relation to the darkly stained intrafusal muscle fibre. (× 1000.)

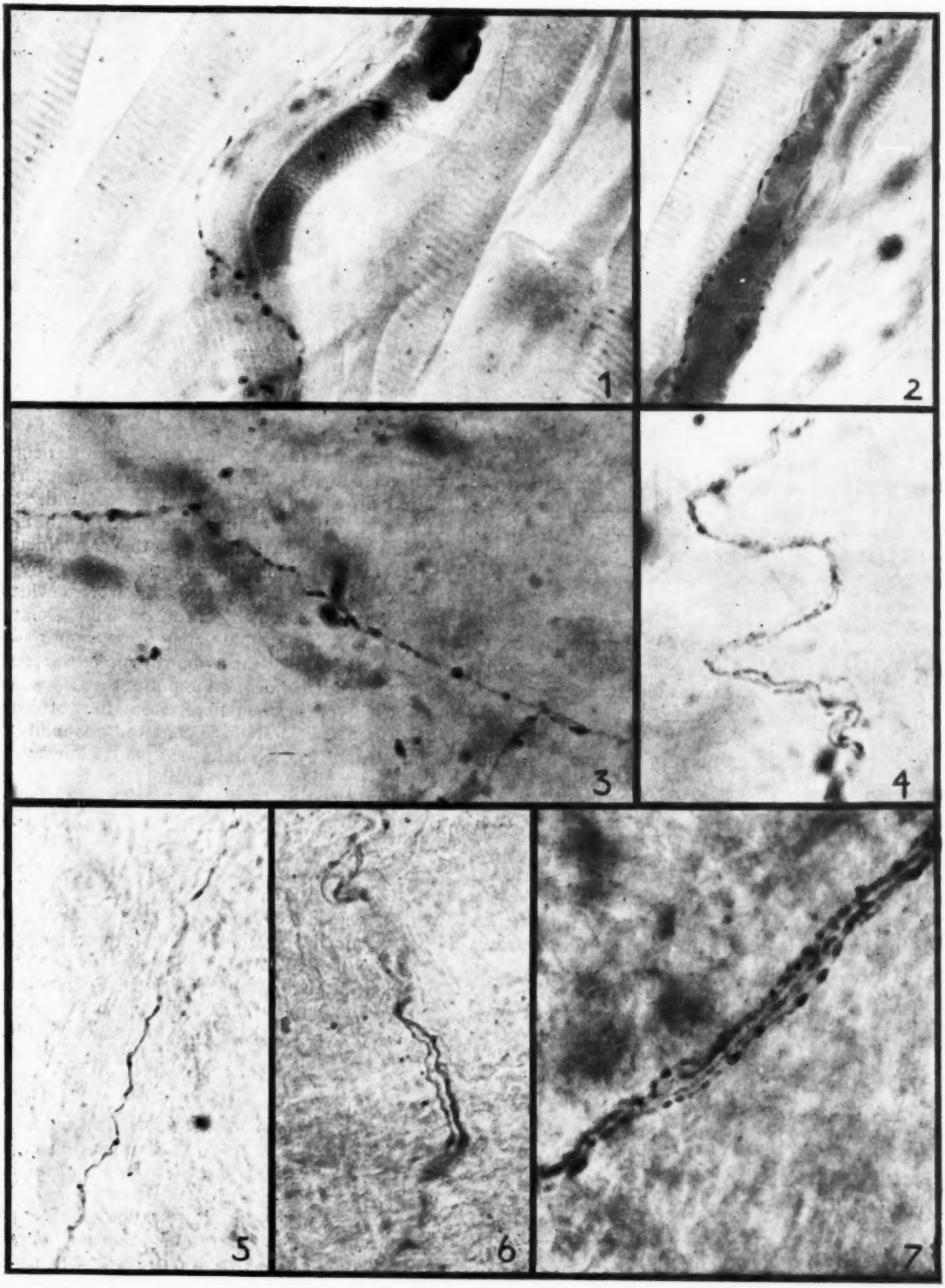
FIG. 2.—Fine beaded nerve fibre in a lumbrical muscle. The fibres in both Fig. 1 and Fig. 2 have no relation to blood-vessels. (× 1000.)

FIG. 3.—Isolated beaded fibre in fascial sheath of neck muscle. Compare with Figs. 4 and 7. (× 850.)

FIG. 4.—Interweaving nerve fibres from another part of the same specimen as shown in Fig. 3. The arrangement is less complex than that shown in Fig. 7. (× 1100.)

FIGS. 5 and 6.—Show respectively an isolated beaded fibre from the periosteum of the tibia, and a pair of interweaving fibres from another part of the same specimen. (× 350.)

FIG. 7.—Leash of fine beaded nerve fibres in human skin from the chest removed following local injection of methylene blue. (× 950.) Note interweaving of adjacent fibres.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PHYSIOLOGICAL MECHANISMS UNDERLYING THE ELECTRICAL ACTIVITY OF THE BRAIN *

BY

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Eighteen years after the first detailed work appeared on the electrical activity of the brain (Berger, 1929) we have still no adequate understanding of its mechanism. There have been many hypotheses, and to review all the supportive data for each would be too space-consuming, but since they are described in the journals a reference list may suffice. For example, there is the evidence, based on the observed behaviour of the EEG with rising body temperature and with metabolic stimulants and depressants (Hoagland, 1936), for the dependence of the electrical rhythmicity on continuous steady-state chemical events within the cortical cells. This hypothesis attempts only an explanation of the resting rhythm, and Hoagland (1944) states that the findings should not be interpreted as meaning that the only modifiers of brain wave frequencies are necessarily changes in cell respiration. There is the hypothesis of Gerard (1941) that the EEG is a rhythmic variation of a somatic potential, demonstrated as a steady DC potential difference between the pia, where the axones end, and the area near the ventricle where cells lie (in the frog's brain). Gibbs and others (1940) suggested that the electrical activity of the cortex is a manifestation of the activity of a great number of chemical oscillators having different natural periods.

The hypothesis that interplay between the deeper centres and the cortex is responsible for the alpha rhythm grows out of the work of Bishop (1933, 1936), of Lorente de Nó (1934, 1935), and of Dusser de Barenne and McCulloch (1938). It was suggested that the cortical cells are in continuous interactivity with the thalamic cells ; that each thalamic neurone projects to many cortical cells, and thus, by recurrent paths through their axones, interacts with great numbers of cells in the thalamus ; and that the alpha rhythm may be determined by the delay in these reverberating circuits, or in other words, by the number of synapses involved. However, evidence has been produced by Morison and Dempsey (Morison and Dempsey, 1942 ; Dempsey and Morison, 1942) that the alpha rhythm of the resting cortex is not dependent on impulses travelling along the primary projection fibres from the recognized thalamic nuclei, and this opens the possibility for transmission by separate neuronal pathways of non-specific afferents from undifferentiated thalamic nuclei (Dempsey and Morison, 1942 ; McCulloch, 1947). There are data from Fortuyn and Jasper's experiments on cats which show that rhythmic potentials in the entire cortex can be co-ordinated from a very restricted thalamic area of less than 2 mm. in diameter (Jasper and others, 1946 ; Fortuyn and Jasper, 1947). It has been suggested (Dempsey and Morison, 1942) that this rhythm of 8 to 12 per second activity may result from constant bombardment by subliminal impulses which sum periodically in the cortex rather than a reverberation in a closed circuit.

There is reason to doubt that this mechanism operates for the frequencies faster than the alpha range, since these persist after section of the thalamic radiations (Bishop, 1933 ; Chatfield and Dempsey, 1942), and therefore presumably represent intrinsic cortical activity.

Later work by Morison threw more doubt on the dependence on reverberation involving cortico-thalamic connexions, since an 8–12 per second

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rhythm could be recorded from the thalamus for as long as three days after bilateral decortication (Morison and Bassett, 1945 ; Morison and others, 1943).

Most of these hypotheses have assumed as a premiss that the electrical activity in the brain travels only along an axonal or dendritic pathway, but, as Adrian (1947) has emphasized, there is the possibility that neurones may influence one another not only by impulses in neuronal pathways but by electrical field effects. Such a mechanism in the development of continued rhythmic activity has been demonstrated in isolated neurones, in the spinal cord, and in the brain.

From observations on isolated nerve preparations it has been shown that the action potential of an active portion of nerve can influence a resting portion across an imposed block (Hodgkin, 1937 ; Lorento de Nó, 1939 ; Blair and Erlanger, 1939), and that in certain circumstances activity in one nerve fibre can affect adjacent ones (Hoagland, 1933 ; Katz and Schmitt, 1940). Bremer's (1947) work on spinal cord discharges, in which he found that synchronized beats could be maintained in two adjacent segments although all neuronal connexion between them was severed by complete transection of the cord, supports the concept of a synchronization maintained by electrical spread in the absence of fibre connexions. And in the brain, Libet and Gerard's (1938) finding that after complete transection one half of a frog's brain could influence the beat of the other half, demonstrates a spread of excitation in the absence of any fibre connexion. These same workers (Gerard, 1941 ; Libet and Gerard, 1938 and 1939 ; Gerard and Libet, 1940) have demonstrated that the cortical rhythms of the frog's brain can persist when all synaptic transmission has been blocked by nicotine. In this context O'Leary's (1944) reminder that we are studying potential records from active tracts embedded in electrolytically conducting material is pertinent.

To these hypotheses must be added that of Eccles (1945) and Brooks and Eccles (1947), who have suggested that the brain potentials may result from the delicate poise between excitatory and inhibitory action in the network of Golgi cells in the brain, so that any agent tending to depress cortical activity would tip the balance towards inhibition by converting some excitors into inhibitors, whereas raised excitation would have the reverse effect.

The relative significance of these many hypotheses waits only the uncovering of more facts, and it is probable that each will be found to play some part in contributing to the final explanation. It is not suggested that experiments in human physiology are likely to give the final proof for any hypothesis of a mechanism so complex, but, since any such hypothesis needs to cover the observed data of the EEG in man, perhaps human experiment may yield evidence of a supportive nature.

The Present Study

In the present paper the results of three types of experiment on the human subject will be examined with such an object in view. The experimental data consist of studies of the effect of anoxia, of hypoglycæmia, and of pentothal anæsthesia on the wave frequencies in the electro-encephalogram of the human subject.

Anoxia

In the course of several years' work on the effect of anoxia (or, to be more exact, of hypoxia) on man we have had plentiful opportunity to confirm the original observations of Berger (1934), and of many other workers since that time (Bremer and Thomas, 1936 ; Davis and others, 1938 ; Lennox and others, 1938), that oxygen lack causes the appearance of slow waves in the EEG. Sometimes the change in the EEG trace is visible in the record on inspection by the unaided eye, but the finer developments of this change can better be studied by automatic analysis of the wave complex, since the presence of slower frequencies may sometimes be masked by more prominent waves of higher amplitude. In the present work an electronic analyser of the type designed by Walter has been used.* For a full description of this technique the original publication should be consulted (Baldock and Walter, 1946).

The type of record obtained is seen in Fig. 1. For the sake of simplicity only the EEG trace which is being automatically analysed is reproduced here, although recordings were also made from many parts of the head by a Grass inkwriting oscillograph. The tracing illustrated was recorded from two electrodes, one on the occipital region and one on the parietal region of a normal man who had in this area a strong alpha focus which blocked to a visual stimulus. Throughout this report the alpha band will be defined as frequencies of 8 to 13 cycles per second. Below the EEG is seen the heart rate recording, and below this the frequency analysis of

* This instrument consists of two banks of 24 oscillators, each designed to resonate to a specific frequency. A resonating circuit is available for each of the usual EEG frequencies, 1·5 cycles per second to 30 cycles per second, and each resonator is connected to an integrating circuit and storage condenser. Every 10 seconds a mechanical scanner discharges these storage condensers in turn through the circuit of a recording pen which gives a deflection at each discharge, the height of the deflection being a function of the activity at that frequency. By the device of having a suitably longer pen for the analyser's trace, this can be written immediately over that part of the original EEG of which it is the analysis. As one bank of storage condensers is discharging, the second is charging, so that a continuous analysis in epochs of 10 seconds each is made possible throughout the whole period of the EEG recording.

the 10-second strip of EEG shown here. The height of the peaks in the analyser's trace is a function of the amount of activity at each frequency, a very small pip (approximately equal to the height of the calibration mark for the EEG on the right of the illustration) representing the baseline for each frequency when no signal is being received. The EEG shows a slowing at the level of reduced oxygen as compared with that in air, and the analysis shows a shift of the alpha activity from a predominantly 11 and 10 cycle rhythm, through a stage at 10 and 9 after 13 minutes of low oxygen, to 8 and 9 cycles at 19 minutes and finally to 8 and 7. It will be noticed that the heart rate also has changed, having accelerated from 66 to 90. His capillary blood sugar level at the time of the test was 120 mg. per 100 c.cm.

Such an effect as is shown in Fig. 1 is typical when breathing for a short time a gas mixture moderately low in oxygen content. In a series of some 150 experiments on subjects examined in an anoxia chamber from which the exhaled carbon dioxide was removed, and a further series of 50 in which a mask with a one-way valve was worn for the administration of low oxygen, we have found essentially this same type of response. The latter part of this series has been examined by automatic analysis and we have been interested to study the results in the light of the various hypotheses briefly outlined at the beginning of this paper.

This gradual shift of the alpha activity, with the dominant frequency of the alpha band moving step by step to the slower side, confirms our previous results found by manual analysis, and also those of Engel and others (1944). It differs in detail from the case analysed by the method of Grass and Gibbs (1938) illustrated by Gibbs and others (1940), where the dominant peak in the alpha band remained at the same frequency (although dropping in height) as long as consciousness was maintained, while the energy in the frequencies slower than alpha increased markedly.

Of course, taking isolated moments in time such as are shown in Fig. 1 does not tell us very much about the way the slow waves have developed, and it is of interest to know whether they develop as a gradual deceleration of the normal synchronized beat, such as would be expected were the rate to have a direct relationship with the metabolic activity of cortical cells, or whether they appear as discrete slow frequencies extraneous to the alpha band originating in other, perhaps sub-cortical, cell groups and rising in voltage until they mask persistent alpha.

In Fig. 2 has been plotted the amplitude of the peak (expressed as a percentage of the maximum possible deflection) at each frequency of the analyser's trace as it was found by measurement at approximately one minute intervals throughout the whole experiment in this same subject. When plotted in this way the highest peaks, that is, the frequencies at which there is most activity, are seen to be at 11, 10, and 12 cycles per second in the baseline record, with no significant activity slower than 9 per second. The breathing of 8·5 per cent. oxygen begins at the first vertical line and continues for nearly thirty minutes to the next vertical line. As this period of anoxia progresses there is a slow fall in the 12, 11, and 10 peaks, with an initial increase in 9 cycles per second which later falls as 8 cycles per second activity increases and the peaks in the slower frequency band become more prominent. The heavy dots indicate the highest peak at each minute step, that is, the dominant frequency at that time, and if we follow this through the whole period we see it decelerate gradually from 11 cycles per second through 10 and 9 to 8, and finally to 7 and 6 cycles per second. All activity slower than 9 cycles per second disappears with the first few breaths of air.

In Fig. 3 an experiment on another normal subject in the anoxia chamber has been plotted in a similar manner. The highest peaks during the baseline period in air in this case are 11, 12, and 10 with lesser peaks at 9 and 8, and minimal activity below 8 cycles per second. The breathing of 8·5 per cent. oxygen begins at the first vertical line, and in this case continues for only fifteen minutes. As this period of anoxia progresses there is a slow fall in the 12, 11, 10, and 9 cycle peaks, little change at 8 cycles, and a marked rise in the frequencies slower than 8. The dominant frequency at each minute step (again indicated by the heavy dots) falls from 12 through the intermediate frequencies to 6 and 5 cycles per second. There was no significant activity slower than 3 cycles at any time in this record. In the last minute of anoxia there is little evidence of persistent alpha, but it returns with spectacular rapidity with the first few breaths of air, and there is a simultaneous disappearance of the slow activity.

Looked at in this way the data are suggestive of a slow deceleration of the synchronized beat of the cell group under observation rather than an eruption of slow waves among persistent alpha activity, but there are some assumptions here the validity of which need to be established by experiment. One is that the change in the relative heights of the peaks represents a change in activity. This arises from our ignorance as to whether a decrease in the prominence of the alpha band in an original EEG tracing represents a decrease in electrical

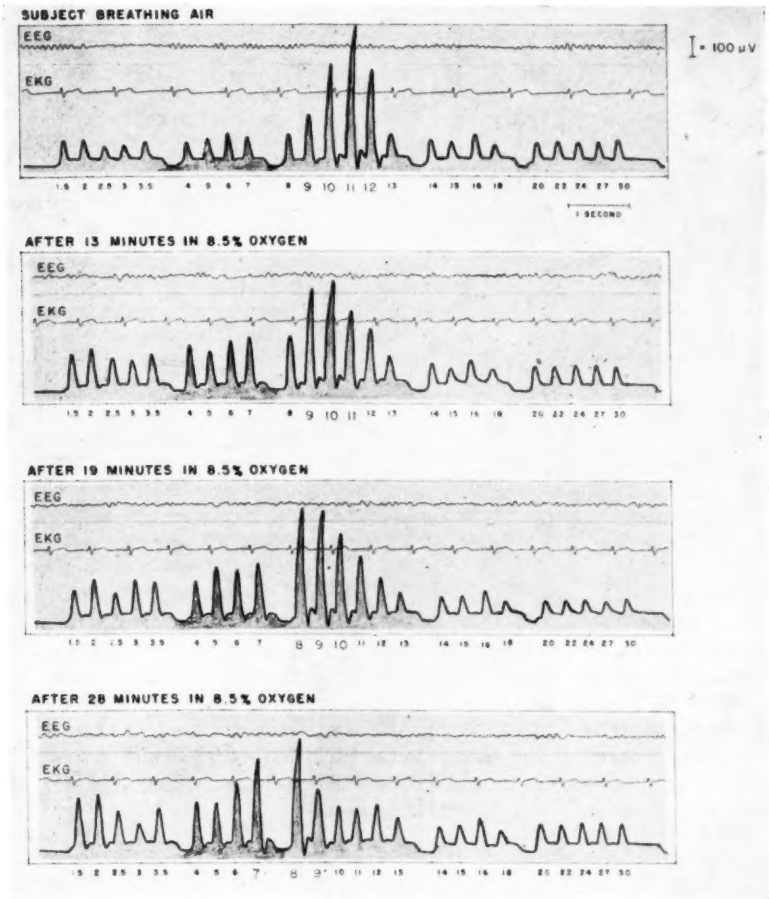


FIG. 1.—*Effect of anoxia on EEG frequencies.* Electroencephalograms, with simultaneous automatic analysis, recorded between two scalp electrodes, one over the parietal and the other over the occipital region of the left hemisphere of a normal man. For clarity only that EEG tracing which was being analysed is reproduced here. The second channel records the heart rate. The frequency represented by each excursion of the analyser's trace is indicated, by the number below it.

activity or whether it indicates a lesser degree of synchronization of the same amount of activity. Only experiment can decide the issue. Another question is whether the observations charted here are indices of the activity of a given synchronised cell group rather than a changing interplay of many independent sources each contributing its own frequencies to the composite picture. The view that Fig. 1 represents a deceleration of the rate of beat of a cell-group entity is supported by the fact that opening the eyes, which blocks the activity in the alpha band, produced blocking of the slower frequencies at 6, 7, and 8 cycles per second later in the experiment when the effect of anoxia was operating. This problem can be further met by making use of interchannel analysis (as described by Baldock and Walter, 1946). By this method only those potential changes which are out-of-phase in the two channels reach the analyser. By searching with electrodes on the head, a position can be found for the electrode which is common to the two channels, where the analysis shows a strong alpha rhythm, out-of-phase in the two channels and blocked by visual stimuli. Presumably such a positioning of the electrode then approximates very closely to an alpha focus. This method has been used in all the later work.

It is known that the cortex is more vulnerable to anoxia than the subcortical and phylogenetically older areas of the brain (Heymans and others, 1934 ; Sugar and Gerard, 1938) and the EEG data just discussed might well point to a slackening in metabolic rate of cortical cell respiration, but it might also indicate a decreasingly influential role of the cortex in a cortico-thalamic interplay. We have not carried any of our experiments on human subjects to an oxygen level low enough for consciousness to be lost as a result of anoxic anoxia. We have had one subject who, in a sitting position, fainted after some minutes of breathing a mixture low in oxygen although the oxygen content did not go below 10·5 per cent. and his capillary blood sugar

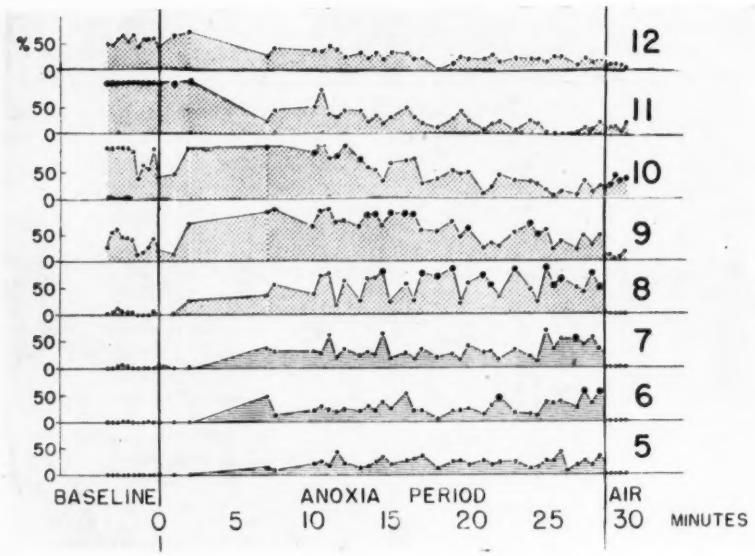


FIG. 2.—*Progression of EEG changes in anoxia.* Chart depicting the height of the peak at each frequency of the analyser's trace from 5 to 12 c/s during a period of anoxia. With the exception of four and a half minutes near the beginning of the experiment the plots have been made at approximately one-minute intervals. The period of anoxia began at the first vertical line and ended at the second. The heavy dots indicate the dominant frequencies at each given moment in time. This is the same experiment and the same electro-encephalogram as that shown in Fig. 1.

level was 113 mg. per 100 c.cm. Here presumably anoxæmia produces a more sudden oxygen lack (as well as a glucose lack and accumulation of carbon dioxide) due to the insufficient blood flow, in contrast to the slowly decreasing supply of oxy-hæmoglobin in the circulation in anoxic anoxia. And if loss of consciousness indicates a depression of the cortex so that thalamo-cortico-thalamic circuits are now disrupted, the EEG might be expected to record waves originating in deeper centres.

The EEG findings in this case are shown in Fig. 4. Here the more exact localization of an alpha focus was made by interchannel analysis as described above. In this experiment the recording paper was being run at half speed to save paper. Again for the sake of clarity only the original tracings of which the interchannel analysis is being made are reproduced here, although simultaneous recordings were also made from other parts of the head. As would be expected at this blood sugar level and with such a mild degree of oxygen lack, there was little change in the EEG except for some occasional 5 and 6 per second activity. At the twelfth minute there was a transient increase in the height of some of the alpha peaks and the appearance of some 4 to 7 cycle activity ; at this time the subject began to show marked pallor and profuse sweating, and his pulse became weak and slow. He complained of nausea, and shortly afterwards (thirteen and a half minutes after he began to breathe the mixture low in oxygen) delta waves appeared in the record and he fainted. He recovered within one minute and the EEG promptly returned to normal.

Thus, in this record, steady activity of alpha frequency is suddenly broken by the eruption of slow waves as the subject faints. This effect is seen more clearly in Fig. 5, where the height of the peaks is charted by the method used in Fig. 2. In this case the delta waves appear to replace the alpha during the short period of unconsciousness. This change in the EEG on fainting closely resembles that described by Romano and Engel (1945) in vasodepressor syncope.

HYPOGLYCÆMIA

Similar methods have been applied to the study of data on subjects whose blood sugar level has been artificially lowered by insulin, since hypoglycæmia is known to affect the EEG (Berger, 1937 ; Hoagland and others, 1937 ; Lennox and others, 1938 ; Gibbs and others, 1940 ; Brazier and Finesinger, 1944 ; Heppenstall, 1944 ; Engel and others, 1944). From a large series of subjects so treated, Fig. 6 is representative of the effect found. In this case the electrode placements and connexions were those indicated in the illustration, with localization of an alpha focus made by interchannel analysis ; the insulin dosage was 25 units.

In the case shown in Fig. 6 the occipital electrode common to the second and third channels was placed in such a position that the recorded alpha activity was out of phase between them. In this illustration the EEG is seen at three levels of blood sugar—98, 60, and 52 mg. per 100 c.cm. The shift of activity from frequencies centering round 11 cycles per second to 7 cycles is clearly seen. At the time of the second EEG sample shown here, 43 minutes after the intravenous injection of insulin, there was no sweating, no subjective sensation, and the heart rate was 88. Sixty-three minutes after the injection the heart rat had dropped to 64 and the subject was

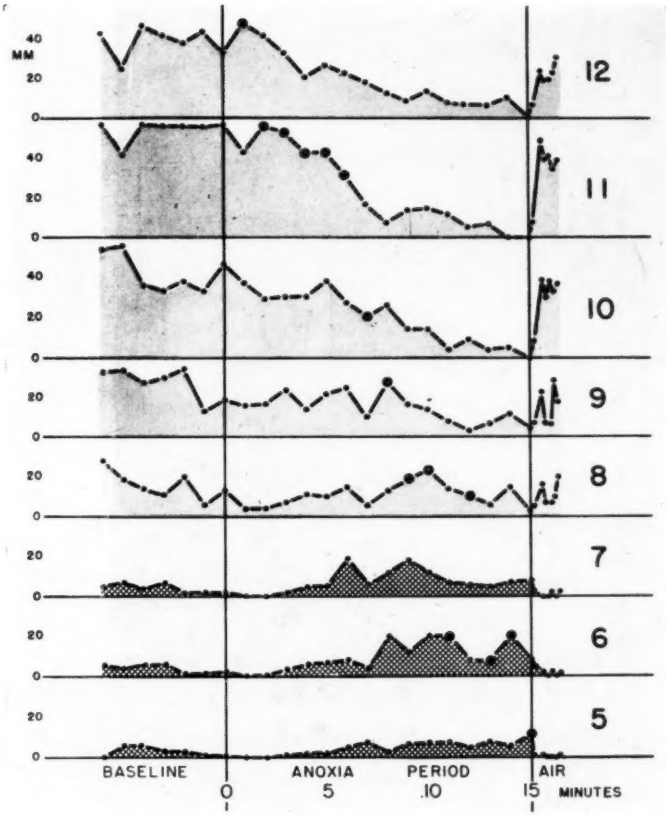


FIG. 3.—*Progression of EEG changes in anoxia.* Chart depicting the height from minute to minute of the peak at each frequency of the analyser's trace from 5 to 12 c/s. Up to the first vertical line the subject was breathing air. In the fifteen minutes between the two vertical lines he was breathing 8·5 per cent. oxygen with 91·5 per cent. nitrogen. At the second vertical line he again breathed air. The EEG was recorded from two scalp electrodes, one over the parietal and the other over the occipital region of the left hemisphere of a normal man. There was at no time any significant activity at frequencies below 5 c/s. The heavy dots indicate the dominant frequency at each given moment in time. The height of the peaks is plotted in millimetres.

sweating profusely. After this he began to recover spontaneously and the EEG also showed some improvement. On the intravenous injection of 50 g. of glucose the clinical signs disappeared almost immediately but the EEG did not return so rapidly to normal.

We have found this delay in recovery of the alpha band in all our cases with mild hypoglycæmia induced by insulin: it is in sharp contrast to the behaviour of delta waves accompanying insulin coma, which disappear promptly on injection of glucose. The frequency shift in the alpha band does not bear a direct relationship to the sugar level of the circulating blood, and persists long after the autonomic disturbances have ceased. This delay in return of normal cortical activity after intravenous administration of sugar is similar to that found in dogs with insulin hypoglycæmia (Hoagland and others, 1939). It is interesting to note that the individual whose EEG is shown in Fig. 6 had fast activity in the 20 to 30 cycles per second band and that, in contrast to the alpha band, this did not slow as the blood sugar level fell.

In contrast to the effect of mild anoxia where the slowing of the EEG is accompanied by an increase in heart rate, in the insulin effect there is a slowing of the heart rate as well as of the EEG. When the data from the whole experiment are plotted by the method already used in the anoxia experiments the result, given in Fig. 7, shows the same gradual deceleration of rate. This chart also illustrates the incipient spontaneous recovery and the delayed response to glucose injection: 15 minutes after the glucose was given, there is very little activity at 11, 12, and 13 cycles per second although the blood sugar at this time was 232 mg. per 100 c.cm. Although this subject had a less regular EEG pattern than those whose records are charted in Figs. 2, 3, and 5, with more minute-to-minute variation, the general trend shows through quite clearly.

At the beginning most of the activity was at 11, 12, and 13 cycles per second. As the insulin began to take effect 9 and 10 cycles per second activity increased, until finally almost all these frequencies were replaced by 6, 7, and 8 cycle waves. At about seventy minutes after the injection the effect of the insulin spontaneously began to wear off, and at eighty minutes the recovery was accelerated by the intravenous injection of glucose.

This gradual shifting of the activity down the frequency range towards the slow side confirms our

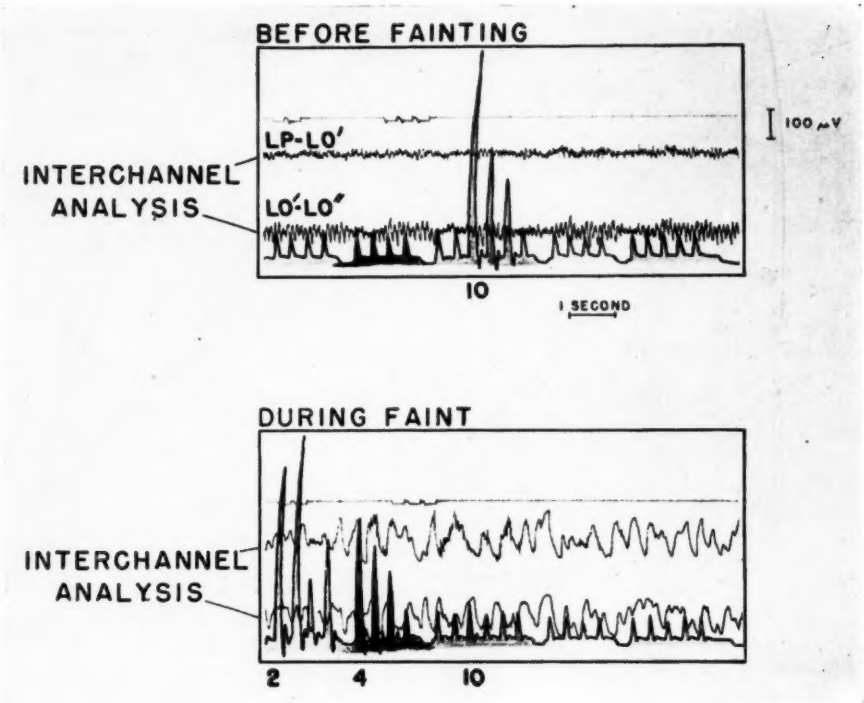
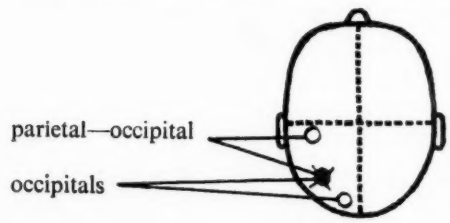


FIG. 4.—*Changes in EEG during a faint.* The electrode placements and connexions were those indicated in the diagram. Interchannel analysis is of the activity out-of-phase between the two channels, that is, of an alpha focus at X. For clarity only these two channels are reproduced here. Recordings were made at a paper speed of 15 mm. per second.



The frequency of the most prominent peaks in the analyser's trace is indicated by the numbers below them. The EEG was analysed for frequencies between 2 and 30 c/s.

previous findings by manual analysis (Brazier and others, 1944), and also those of Engel and others (1944), who used a different form of manual analysis. It is also in agreement with the case illustrated by Gibbs and others (1940) depicting the change found in the Grass frequency spectrum with a similarly small lowering of the blood sugar level (in their case from 105 to 74 mg. per 100 c.cm.). Their illustration shows a shift of the dominant alpha peak from 10 to 9 cycles, with a rise in the amplitude of the 8 and 7 cycle peaks. The result is, however, at variance with these authors' statement that "there is no definite shift in peaks until the sugar level falls below 29 mg. per 100 c.cm."

The mode of development of the slow activity resulting from mild anoxia and from mild hypoglycæmia is so similar that it suggests a similar underlying mechanism, one in which a cell-group entity is responsible for the effects seen. Opening the eyes has the same effect on the slow activity in hypoglycæmia as in anoxia, for the activity centering around 7 cycles per second at the low blood sugar level is blocked by opening the eyes, just as is the original alpha band before the insulin takes effect. The mode of appearance of slow waves in the record of the subject who fainted is, however, strikingly different. Here, with loss of consciousness, there is a momentary loss of all alpha frequencies and replacement by delta waves. In the case illustrated in Figs. 4 and 5 the recording was being made from an alpha focus localized by phase-reversal and interchannel analysis, and such a result suggests that the cell group responsible for the alpha activity at this focus has, on loss of

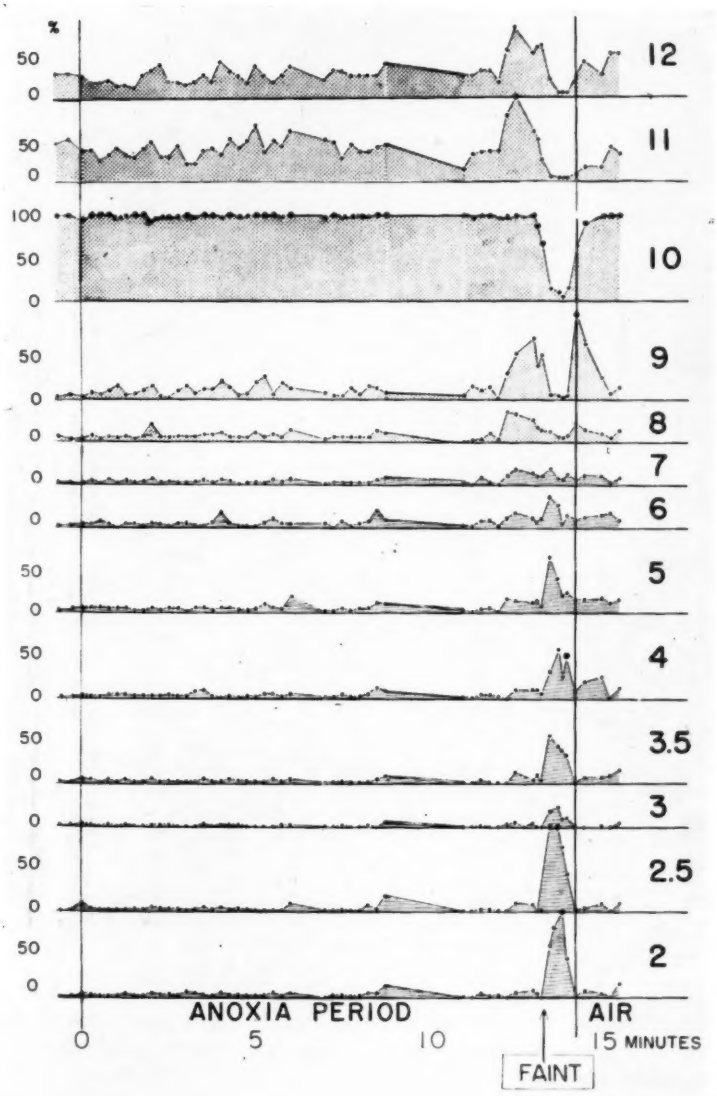


FIG. 5.—*Progression of EEG changes during a faint in* 10·5 *per cent. oxygen.* Chart showing the height of the peak at each frequency of the analyser's trace from 2 to 12 c/s in an EEG recorded during a short period of mild oxygen lack, at the end of which the subject fainted. With the exception of a two-minute period beginning at the ninth minute, during which the subject was being interrogated, the plots have been made at half-minute intervals. This is the same individual and the same electro-encephalogram as that shown in Fig. 4.

consciousness, become disorganized or depressed in such a way as to release slower rhythms from deeper structures.

PENTOTHAL ANÆSTHESIA

We have been interested to study by similar methods of analysis the EEG changes accompanying loss of consciousness induced by anæsthetic drugs. We have in the first place used sodium pentothal, since the mode of action of barbiturates on the brain has been worked out in more chemical detail than that of many other anæsthetics.

The procedure followed has been to give the pentothal by intravenous injection of a 2 per cent. solution given at a rate calculated to induce third-stage anæsthesia within about three minutes. In the course of an investigation on the mode of action of pentothal we have recorded electro-encephalograms in 112 experiments on 75 subjects. We have found the EEG changes to be strikingly consistent: in every case the first change is the appearance of fast activity, usually of rather high voltage, followed later by slow waves (Brazier and others, 1945). The fast activity first appears during the first stage of anæsthesia and is not seen while the subject is truly alert but only when there is some degree of clouding or euphoria. In most cases the fast waves increase in amount as the first stage of anæsthesia progresses.

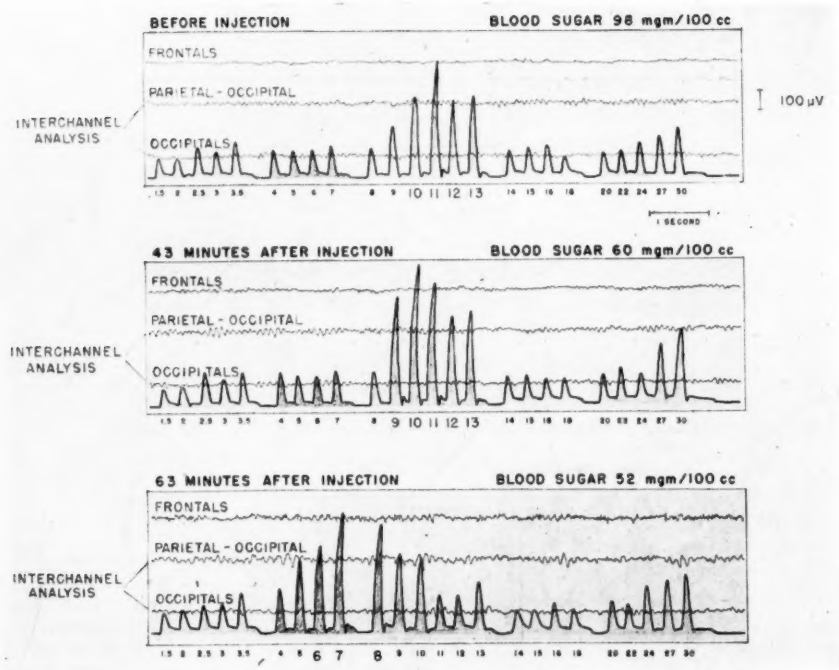
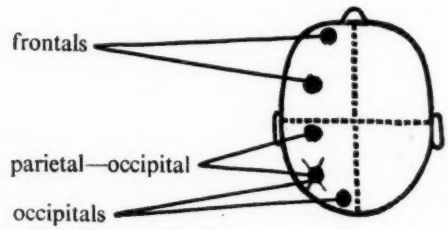


FIG. 6.—*Effect of insulin on EEG frequencies.* Electro-encephalograms of a normal man with simultaneous automatic analysis. The electrode placements and connexions were those indicated in the diagram. Interchannel analysis is of the activity out-of-phase between the second and third channel, that is, of an alpha focus at X. The frequency represented by each excursion of the analyser's trace is indicated by the number below it.



Analysis shows them to have a frequency usually of 24 to 27 cycles per second.

The second change regularly occurs when the subject becomes unconscious, that is, when he loses contact with his environment and enters the second stage of anæsthesia. Concurrently with this loss of consciousness the fast waves in the EEG disappear and are supplanted by slow waves.

One example of these changes is seen in Fig. 8. In this illustration EEG recordings are shown from three parts of the head, as indicated in the legend accompanying the figure, and the simultaneous analysis of the strong alpha focus in the third channel is superimposed. During the first stage of anæsthesia, while this subject was euphoric, activity was mostly in the fast frequencies from 20 to 27 cycles per second. When he became unconscious, bands of slow waves centering around 2·5 and 6 cycles per second dominated the record.

In this individual the alpha frequencies have been almost extinguished, but it is common to find these persisting even in the second plane of the third stage of anæsthesia. An example is shown in Fig. 9. In this illustration, for clarity only the EEG tracing which is being analysed is reproduced. It is from an alpha focus in the parieto-occipital region. The disappearance of the fast waves when the delta and slow frequencies come in is again seen and the persistence of alpha frequencies is marked.

To illustrate more clearly the sequence of changes in EEG frequencies which accompany shifting levels of consciousness in pentothal anæsthesia a different method of charting has been used. This is seen in the analysis of an alpha focus in another EEG given in Fig. 10. The chart reads from top to bottom, and the width of the white band indicates the spread of frequencies found in the EEG by automatic analysis, plotted every half-minute throughout the whole experiment. The black spots

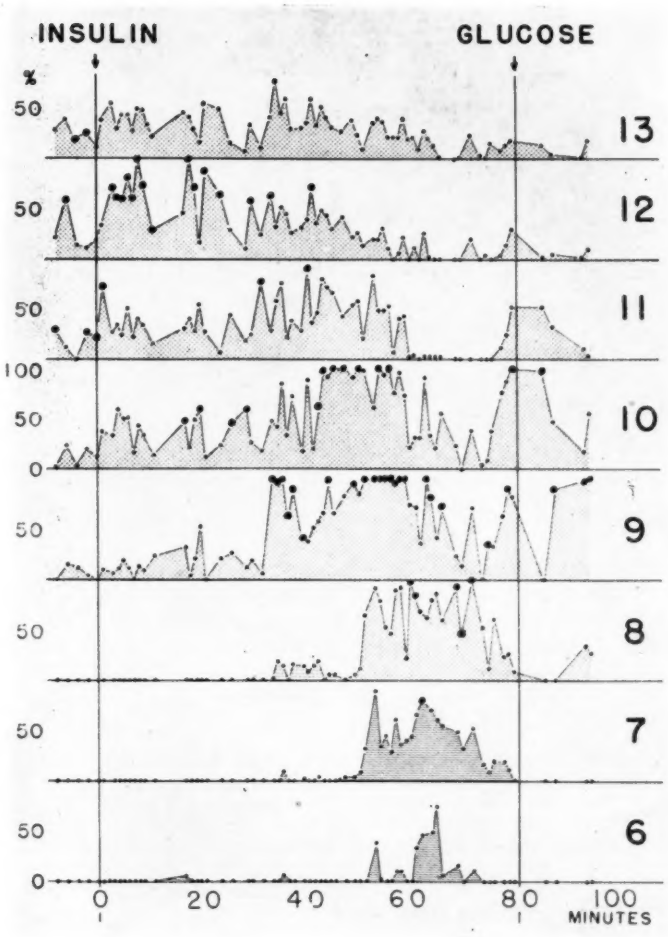


FIG. 7.—*Progression of EEG changes in hypoglycæmia.* Chart depicting the amplitude of the peak at each frequency of the analyser's trace from 6 to 13 c/s from minute to minute in an EEG recorded during and after the intravenous injection of insulin. This is the same experiment and the same electro-encephalogram as that shown in Fig. 6.

represent the actual frequencies present as indicated on the abscissa, and the larger black dot the dominant frequency of each recorded sample. The column on the right indicates the levels of anæsthesia from its induction to the second plane of the third stage, and then the gradual return to a normal state of consciousness.

There are certain quite striking data to be seen in this chart. The development of the fast frequencies in the EEG begins during the first stage, when the cortex is still functioning and when the subject is still conscious. These abnormal fast frequencies are not found when the subject is truly alert, but, as noted above, are evident only when there is some degree of clouding or euphoria. Up to this point all activity in the EEG is in the alpha range. The coincidence of loss of consciousness and the first appearance of slow waves is dramatic, and the fast activity is gone at the same moment. It will be noted that at no time are alpha frequencies absent from the record, although in these cases, when the subject is unconscious, lifting the lids and shining a light directly into the eyes does not block out the activity in the alpha band.

In all cases on emergence from pentothal anæsthesia fast activity returns some time before the slow waves disappear. Neither the EEG changes nor the clinical signs associated with the various planes and stages of anæsthesia are as clear during emergence as they are during induction.

The distribution of frequencies on loss of consciousness from pentothal is different from that found in our record of the subject who fainted, and whose record has been described above. When the EEG frequencies of his record are plotted by the method used in Fig. 10, the distribution is found to be almost entirely within the alpha band until shortly before he faints. Some 4 to 7 cycles per second then appear in the record, and as he faints the alpha disappears for the first time and delta

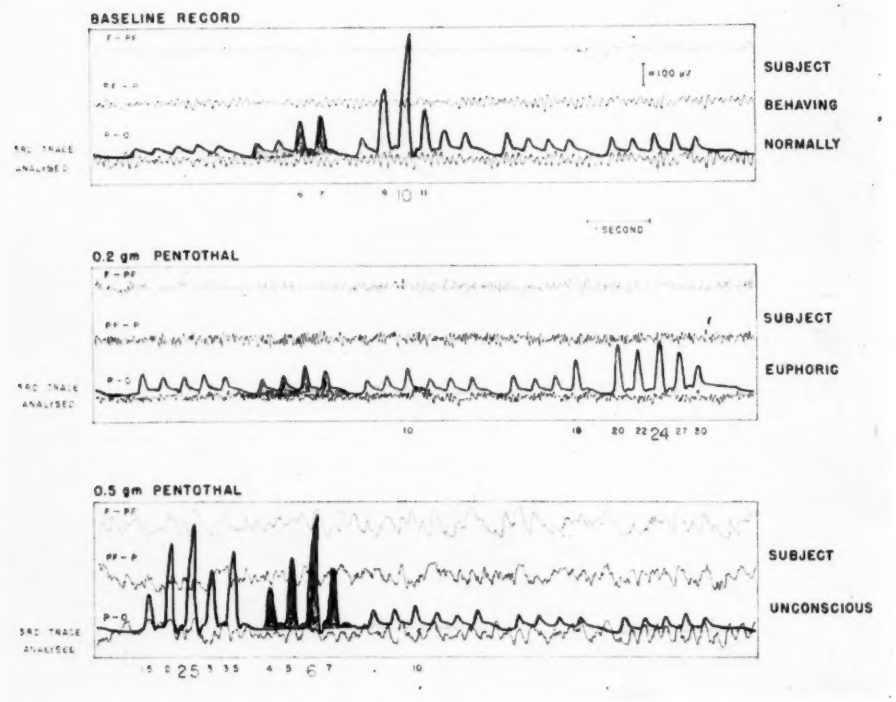
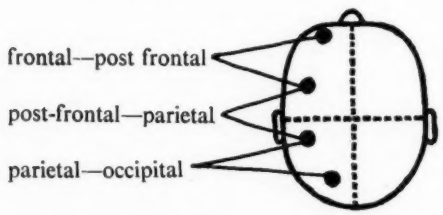


FIG. 8.—*Effect of pentothal on EEG frequencies.* Electro-encephalograms of one individual recorded from electrodes placed and connected as indicated by the diagram. The analysis is of the EEG tracing shown in the third channel of each strip. The frequency of the most prominent peaks in the analyser's trace is indicated by the numbers below them.



waves replace it (Fig. 11). The faint lasts less than a minute; on recovery alpha frequencies return and the delta disappears, but a slow band of activity between 4 and 7 cycles per second persists. EEG recording could not be continued for more than a minute following recovery, because of the desirability of moving the subject. At no time was there any EEG activity at frequencies faster than 13 cycles per second.

Discussion

The striking similarity between the effect on EEG frequencies of inadequate supplies of oxygen and of sugar is understandable on a basis relating these potentials to brain respiration rates, since these two substances play the major roles in cerebral metabolism. That lack of either produces the same effect is in keeping with several known facts, such as that cerebral oxygen uptake is decreased at low levels of blood sugar and increased on administration of sugar (Himwich and others, 1939), and that the action of hypoglycæmia on the EEG can be offset by the inhalation of pure oxygen (Gellhorn and Kessler, 1942).

The data reported here on oxygen lack and on hypoglycæmia at levels where consciousness is retained show a progressive slowing of the alpha rhythm suggestive of a deceleration of the synchronized beat of a uniform neurone population. This view is further supported by the observation that opening the eyes blocks the observed activity in the EEG even when this has slowed to frequencies outside the alpha band. Such observations would be covered by the hypothesis that there is a correlation between the rate of metabolism in the intrinsic cells of the cortex and the relative alpha frequency.

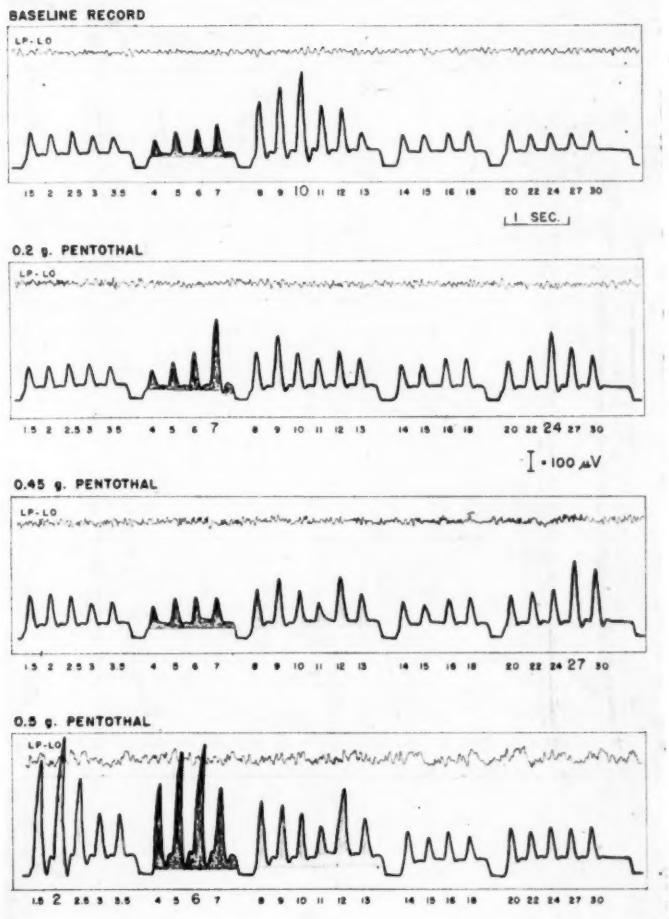


FIG. 9.—*Effect of pentothal on EEG frequencies.* Electro-encephalograms, with analysis, recorded between two scalp electrodes, one over the parietal and the other over the occipital region of the left hemisphere of an individual before and during pentothal anæsthesia. For clarity only that EEG tracing which is being analysed is reproduced here. The frequency represented by each excursion of the analyser's trace is indicated by the number below it.

That the cortical cells are likely to be implicated before the thalamic nuclei is suggested by the work of, among others, Sugar and Gerard (1938), who, in a comparative study of various regions of the brain (in cats), established that the cortex was more vulnerable to anoxia than the thalamus, and that this paralleled the oxygen requirements determined directly by Dixon and Meyer (1936).

Interpreted in terms of reverberation in thalamo-cortical circuits one would need to consider not only the thalamic and cortical cell bodies, but the axones and synapses in the neurone chains. Synaptic conduction has proved to be very resistant to anoxia, at least as much so as fibre conduction (Bronk and others, 1938). From studies of fibre conduction in peripheral nerve it is known that the spike potential which is associated with the passage of the nerve impulse is extremely stable to changes in metabolic environment; it is the afterpotentials which are affected by anoxia, and, as Erlanger and Gasser (1937) have demonstrated, a nerve can be brought by mild asphyxia to a state in which it produces good single spikes but poor negative afterpotentials so that the preparedness of the fibre to receive repetitive impulses is impaired. Such an impairment would clearly affect any process involving the summation of trains of action potentials to produce waves of alpha frequency. Similar conditions apply to the cell bodies: any mechanism relying on summation of repetitive stimuli would result in a rate of discharge dependent not only on the frequency of these impulses but on the rate of oxidative recovery in the neurones under bombardment. Bartley and Bishop (1933), in their original work on responses of the optic cortex, expressed the opinion that cortical cells play a more dominant role than the fibres in the electrical activity. They based this not only on the vulnerability of the cortical potentials to degrees of anæmia and anæsthesia to which fibres would be impervious,

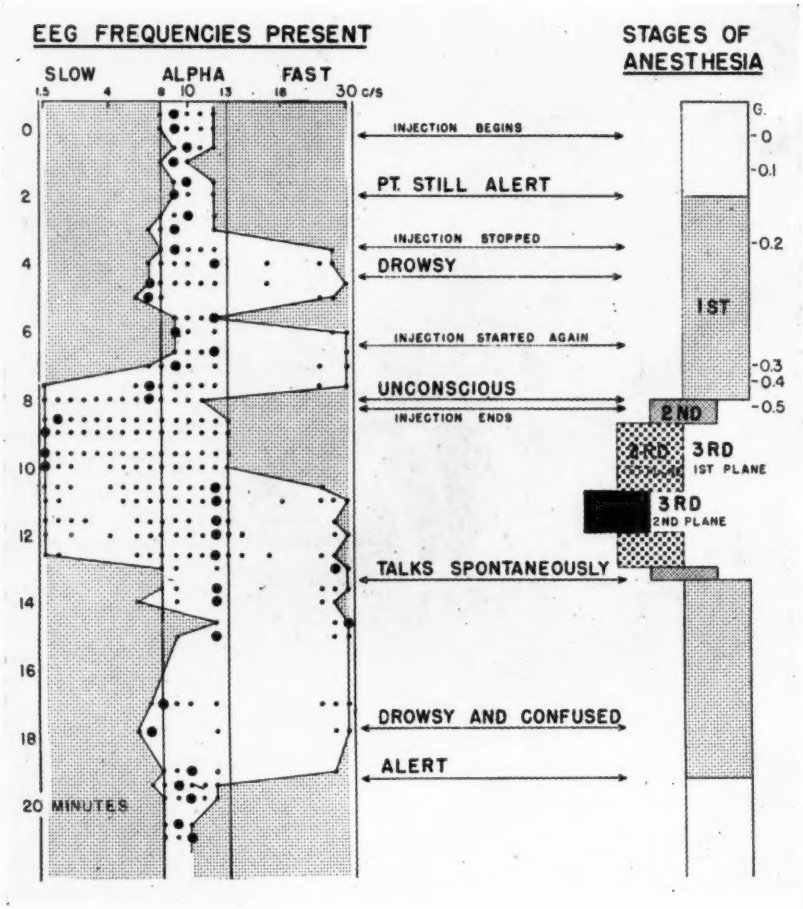


FIG. 10.—*The EEG in pentothal anæsthesia.* Chart showing which frequencies were present in the EEG of an individual throughout a period of anæsthesia induced by pentothal. The experiment begins at the top of the chart and proceeds vertically downwards. Each dot indicates a significant peak in the analyser's trace at the frequency indicated on the abscissa. The heavy dots indicate the dominant frequency of the EEG in each plotted sample. The EEG data are charted at thirty-second intervals throughout most of the experiment. The concurrent stages of anæsthesia are charted on the right of the diagram and follow the same time scale as the EEG from the top of the chart to the bottom.

but also on the magnitude of the potentials recorded, which they thought too great to be accounted for by the summation of fibre potentials in a tissue environment found by them to act as a shunt.

Turning back to the data reported here, one finding would be at variance with this line of interpretation. In the one case illustrated in Fig. 6 there is some activity of beta frequency ; unlike the alpha activity present in the same record this does not slacken in rate as the blood sugar falls, an observation which is difficult to reconcile with the theory that the cortical cell plays the dominant role in frequency determination if these beta frequencies are to be considered as representing intrinsic cortical activity (Chatfield and Dempsey, 1942). However, this is an observation on a single individual and need not be given importance until confirmed.

The data from the pentothal studies are more complex. From biochemical studies of the metabolism of glucose by brain slices the sequence has been found to progress through pyruvate, lactate, glutarate, and other metabolites to oxalacetate. At each step two hydrogen atoms are detached by the enzyme action of dehydrogenases. It has been clearly demonstrated *in vitro* (Quastel, 1939) that the inhibitory action of barbiturates on the oxidation by the brain of glucose, lactate, and pyruvate is by the inactivation of this dehydrogenase activity. On this basis it could be postulated that the initial change to fast frequencies could be due to increased intracellular acidity caused by accumulation of unoxidized acid metabolites (for it is known that lowering the *p*H of blood raises the frequency of the alpha rhythm). If this were the mechanism it would appear that a point is reached as the depth of anæsthesia progresses at which the initial effect due to the accumulation of acid metabolites is overwhelmed by the second effect due to the slowing up of the principal chemical reaction caused by the accumulation of its metabolites.

If, on the other hand, the rhythm of the EEG were dependent on reverberation in thalamo-cortical

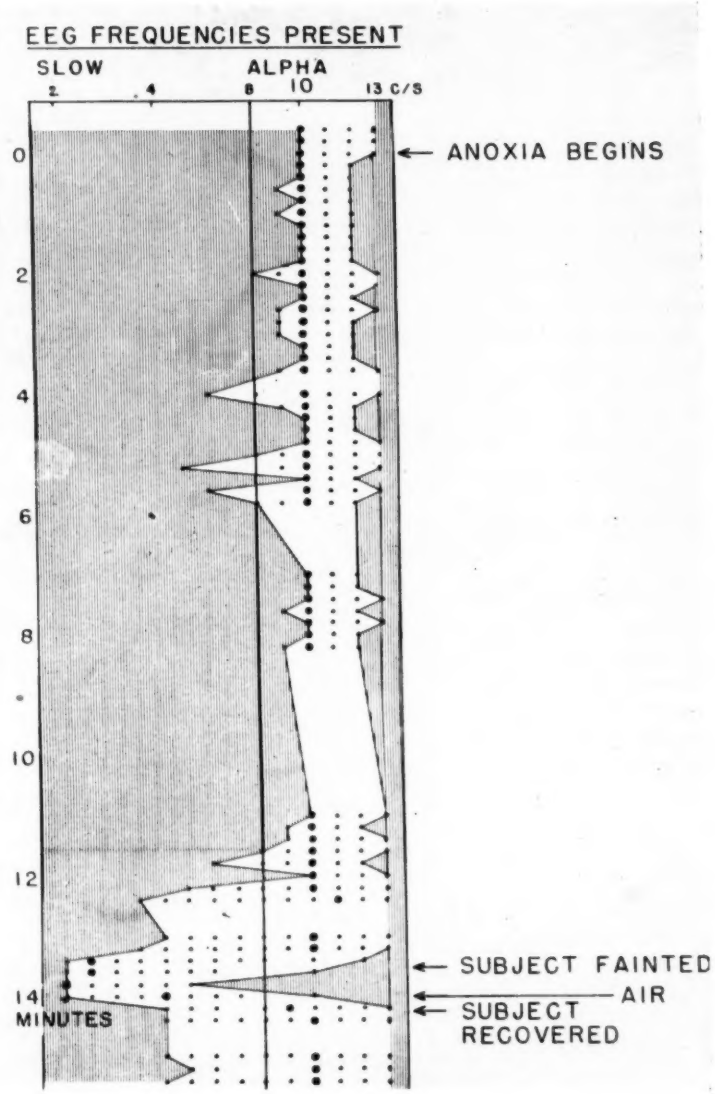


FIG. 11.—*The EEG during a faint.* Chart showing the distribution of frequencies present in the EEG of an individual throughout a short period of mild anoxia and during a faint. The observations begin at the top of the chart and proceed vertically downwards with time. Each dot indicates a significant peak in the analyser's trace at the frequency indicated on the abscissa. The heavy dots indicate the dominant frequency of the EEG in each plotted sample. This is the same individual and the same electro-encephalogram as in Figs. 4 and 5.

circuits, the two stages of EEG change might represent two loci of attack by the drug. The studies of Etsten and Himwich (1946) have demonstrated the pattern of pentothal anæsthesia to be a descending depression of cerebral oxidations starting with the cerebral hemispheres and progressing down to the lower parts of the brain. During the first stage of anæsthesia (when the EEG shows fast frequencies) there is slight depression of the cortex but it is still the controlling centre. The cortical cells would therefore presumably still be active in any thalamo-cortical circuit. When the subject loses consciousness the cortex has become suppressed and predominant control is by the subcortex. It is at this stage, when the thalamic levels presumably take control, that the slow waves appear in the EEG.

The possibility that the loss of consciousness in pentothal anæsthesia is due to the blocking of afferent impulses from the periphery rather than to a depression of the cortex needs also to be considered. It has been noted above that shining a light into the eyes of subjects under pentohal anæsthesia does not block any EEG rhythms although some are usually of the frequencies defined as alpha (8 to 13 cycles per second). Such a concept would introduce the picture of a cortex isolated by the anæsthetic rather than depressed by it. A different mechanism has been advanced by Brooks

and Eccles (1947) as an extrapolation of their theory of inhibition, namely that narcotics would, by depressing the excitation in the Golgi cells, augment the inhibition, and that lowered cortical activity due to deprivation of incoming sensory impulses would convert excitatory Golgi cells into inhibitors.

Clearly more data are needed. More cannot be said at the present stage of our knowledge. Human electro-encephalography alone cannot answer all the questions, but its role should not be minimized since it is a study of the brain in its natural environment. And it can give some answers: for example, the data from the experiments with mild hypoxia and hypoglycæmia demonstrate that at levels where there is no loss of consciousness the slow activity in the EEG is not a masking of persistent alpha by the eruption of slow activity. The data are evidence for a unitary effect, for a progression of frequency change in the same neurone population, although the anatomical identification of these units cannot be made from experiments of this nature.

In summary, the data reported here are consistent with a postulate that the alpha rhythm results from the repetitive action of cells in neurone chains, that the rate can be modified within certain limits by metabolic changes in the respiration of cortical cells, that it can be disrupted by any agent which inactivates a link in the chain, and that it is thrown out of synchrony by the arrival of action potentials originating as sensory impulses.

Summary

The results are reported of continuous automatic frequency analysis of electro-encephalograms recorded from human subjects throughout periods of: (1) mild hypoxia without loss of consciousness; (2) mild hypoglycæmia without loss of consciousness; (3) loss of consciousness induced by pentothal anæsthesia; (4) loss of consciousness occurring briefly in one case of fainting.

The data are reviewed in the light of existing hypotheses as to physiological mechanisms, and evidence is presented to show that the observed frequency changes caused by oxygen lack and low blood sugar level are changes in the same neuronal population rather than a replacement by activity from other cell units. The changes in pentothal anæsthesia are more complex and are discussed in comparison with those found in loss of consciousness in the absence of the drug.

The data reported here have been accumulated during the course of several studies in progress in Dr. Stanley Cobb's Department at the Massachusetts General Hospital. The results are the outcome of the collaboration of a team of workers to whom the author is indebted. She especially wishes to thank Dr. J. E. Finesinger and Dr. H. H. W. Miles of the Department of Psychiatry, Dr. J. H. Tucci of the Department of Anæsthesia, and Dr. R. S. Schwab of the Electro-encephalographic Laboratory. Miss M. N. Gray, Mrs. G. Lothrop, and Mr. J. U. Casby have given invaluable technical help.

References

Adrian, E. D. (1947). *Brain*, **70**, 1.
Baldock, G. R., and Walter, W. G. (1946). *Electron. Engng.*, **18**, 339.
Bartley, S. H., and Bishop, G. H. (1933). *Amer. J. Physiol.*, **103**, 173.
Berger, H. (1929). *Arch. Psychiat.*, **87**, 527.
——(1934). *Ibid.*, **102**, 538.
——(1937). *Ibid.*, **106**, 165.
Bishop, G. H. (1933). *Amer. J. Physiol.*, **103**, 213.
——(1936). *Cold Spr. Harb. Symp. quant. Biol.*, **4**, 305.
Blair, E. A., and Erlanger, J. (1939). *Amer. J. Physiol.*, **126**, 97.
Brazier, M. A. B., and Finesinger, J. E. (1944). *J. clin. Invest.*, **23**, 303.
——, ——and Schwab, R. S. (1944). *Ibid.*, **23**, 313.
——, ——(1945). *Arch. Neurol., Psychiat., Chicago*, **53**, 51.
Bremer, F. (1947). Communication to the First International EEG Congress. London.
——and Thomas, J. (1936). *C.R. Soc. Biol. Paris.*, **123**, 1256.
Bronk, D. W., Larrabee, M. G., Gaylor, J. B., and Brink, F. (1938). *Amer. J. Physiol.*, **123**, 24.
Brooks, C. McC., and Eccles, J. C. (1947). *Nature*, **159**, 760.
Chatfield, P. O., and Dempsey, E. W. (1942). *Amer. J. Physiol.*, **135**, 633.
Davis, P. A., Davis, H., and Thompson, J. W. (1938). *Ibid.*, **123**, 51.
Dempsey, E. W., and Morison, R. S. (1942). *Ibid.*, 293 and 301.
Dixon, T. F., and Meyer, A. (1936). *Biochem. J.*, **30**, 1577.
Dusser de Barenne, J. G., and McCulloch, W. S. (1938). *J. Neurophysiol.*, **1**, 176 and 364.
Eccles, J. C. (1945). *Nature*, **156**, 680.
Engel, G. L., Romano, J., Ferris, E., Webb, J. P., and Stevens, C. D. (1944). *Arch. Neurol. Psychiat., Chicago.*, **51**, 134.
Erlanger, J., and Gasser, H. S. (1937). Electrical signs of nervous activity. Univ. of Pennsylvania Press. Philadelphia.
Etsten, B., and Himwich, H. E. (1946). *Anesthesiology*, **7**, 536.
Fortuyn, J. D., and Jasper, H. H. (1947). Communication to the Seventeenth International Physiological Congress. Oxford.
Gellhorn, E., and Kessler, M. (1942). *Amer. J. Physiol.*, **136**, 1.
Gerard, R. W. (1941). *Ohio J. Sci.* **41**, 160.
——and Libet, B. (1940). *Amer. J. Psychiat.*, **96**, 1125.
Gibbs, F. A., Williams, D., and Gibbs, E. L. (1940). *J. Neurophysiol.*, **3**, 49.
Grass, A. M., and Gibbs, F. A. (1938). *Ibid.*, **1**, 521.
Heppenstall, M. E. (1944). *J. Neurol. Neurosurg. Psychiat.*, **7**, 112.
Heymans, C., Jourdan, F., and Nowak, S. (1934). *R. Soc. Biol. Paris*, **117**, 470.
Himwich, H. E., Hadidian, Z., Fazekas, J. F., and Hoagland, H. (1939). *Amer. J. Physiol.*, **125**, 578.

Hoagland, H. (1936). *Ibid.*, **116**, 604.
——(1944). Colloid Chemistry, New York, p. 762.
——(1933). *J. gen. Physiol.*, **17**, 195.
——Rubin, M. A., and Cameron, D. E. (1937). *Amer. J. Physiol.*, **120**, 559.
——Himwich, H. E., Campbell, E., Fazekas, J. F., and Hadidian, Z. (1939). *J. Neurophysiol.*, **2**, 276.
Hodgkin, A. L. (1937). *J. Physiol.*, **90**, 211.
Jasper, H. H., Penfield, W., and Droogleever-Fortuyn, J. (1946). *Proc. Assn. for Research in Nerv. and Men. Dis.* Baltimore. Vol. **26**.
Katz, B., and Schmitt, O. H. (1940). *J. Physiol.*, **97**, 471.
Lennox, W. G., Gibbs, F. A., and Gibbs, E. L. (1938). *J. Neurol. Psychiat.*, **1**, 211.
Libet, B., and Gerard, R. W. (1938). *Amer. J. Physiol.*, **123**, 128.
——, ——(1938). *Proc. Soc. exp. Biol., N.Y.*, **38**, 886.
——, ——(1939). *J. Neurophysiol.*, **2**, 153.
Lorente de Nó, R. (1934). *J. Psychol. Neurol., Lpz.*, **46**, 113.
——(1935). *Amer. J. Physiol.*, **113**, 505.
——(1939). *J. Neurophysiol.*, **2**, 402.
McCulloch, W. S. (1947). *Fed. Proc.*, **6**, 448.
Morison, R. S., and Dempsey, E. W. (1942). *Amer. J. Physiol.*, **135**, 281.
——and Bassett, D. L. (1945). *J. Neurophysiol.*, **8**, 309
——Finley, K. H., and Lothrop, G. N. (1943). *Ibid.*, **6**, 243.
O'Leary, J. L. (1944). in Bucy. P.C. The Precentral Motor Cortex. University of Illinois Press. Chapter III.
Quastel, J. H. (1939). *Physiol. Rev.*, **19**, 135.
Romano, J., and Engel, G. L. (1945). *Psychosom. Med.*, **7**, 3.
Sugar, O., and Gerard, R. W. (1938). *J. Neurophysiol.*, **1**, 558.

THE ROLE OF ACETYLCHOLINE IN SYNAPTIC TRANSMISSION: A CRITICAL REVIEW

BY

D. WHITTERIDGE

(RECEIVED MARCH 19, 1948)

The nature of the mechanism of synaptic transmission has occupied a central place in physiological investigation for the last fifteen years; and, although there are now fewer disputed observations, the interpretations placed on the data seem to be as widely divergent as ever. In his valuable review of the evidence on the mode of action of acetylcholine (subsequently abbreviated as ACh) on the central nervous system, Feldberg (1945) spoke of the problem as "almost solved." A little later Gerard (1946), summing up the symposium on the physico-chemical nature of nervous activity, concluded that "ACh is not critically involved in nerve conduction and we must be reserved in assigning to it a role in junctional transmission particularly within the nervous system." Some new evidence which has appeared in the last few years now helps to define the points at which current views of the action of ACh are almost certainly wrong, and brings into relief earlier observations which support an alternative view.

Action of Acetylcholine in Excitation of Nerve and Muscle

In the central nervous system, exact information about events at single synapses is so difficult to obtain that the habit of arguing by analogy from the peripheral nervous system is ingrained and often profitable. It is, therefore, worth considering what is known of the mode of action of ACh and other mechanisms in the excitation of nerve and muscle.

Depolarization by Acetylcholine.—As soon as it was realized that there is some evidence for the liberation of ACh during excitation along the whole length of nerve fibres, it was suggested that this substance was responsible for the depolarization of the nerve fibre, and that by spreading forward it was responsible for the spread of the impulse. This view is ruled out by the salt bridge experiment of Osterhout and Hill (1930), and by the corresponding experiments on nerve (Hodgkin, 1939). These experiments establish that the local circuits set up between an active and an inactive point on the nerve are themselves sufficient to depolarize and therefore activate the distant point. Spread of the impulse can occur in the absence of the diffusion of any chemical substance. The view of the mode of action of ACh was therefore modified by the suggestion that the principal effect of ACh was to increase the permeability of the cell membrane, and that the effect of electrical excitation of the cell membrane was to produce the liberation of ACh. This was said to permit the depolarization of adjacent points by local flow of current, which again liberates ACh. The transmitting agent is the flow of current, but the current is generated by the release of ACh (Nachmansohn, 1945). If this is interpreted to mean that an increase of permeability due to ACh permits the flow of current generated by some unknown source of E.M.F., this view would at first sight seem to be tenable.

The strongest support for the view that ACh is intimately concerned with processes leading to depolarization comes from the nerve-muscle junction. Cowan (1938) showed that the sartorius muscle could be depolarized to a considerable extent by immersing it in a solution of ACh, and that this depolarization could be prevented by the previous application of curarine. Kuffler (1943) applied ACh locally to the end-plate region in his single nerve-muscle junction preparation, and succeeded in showing that its depolarizing effect is limited to the end-plate region. It neither depolarizes nor sets up nerve impulses on the surface of the muscle itself. Potassium however sets up impulses most readily at the end-plate region, but depolarizes both the muscle fibre and the end-plate.

Action of Anticholinesterases and ACh on Nerve.—The nerve muscle junction and probably the electric organ provide the only established cases of the depolarization of undamaged tissue by ACh, and it is therefore a doubtful assumption to ascribe all excitatory effects of ACh elsewhere to a depolarization.

The main reasons for believing that ACh plays an essential part in the initiation of nervous impulses in peripheral nerve have been summarized by Nachmansohn (1946). In the motor nerves of vertebrates, ACh is liberated by the passage of nerve impulses, conduction is blocked by anticholinesterases, cholinesterase is present in nerve and is highly specific, and choline acetylase, an enzyme system which synthesises ACh, is also present and active. Much argument has taken place over the second proposition, the question at issue being whether the inhibitory effect of anticholinesterases, particularly diisopropyl fluorphosphonate, or DFP, on the enzyme system is exerted *pari passu* with its effects on the blocking of impulses. The results of Bullock, Grundfest, Nachmansohn, Rothenburg, and Sterling (1946) suggest that these two effects do in fact run parallel. The essential step in this argument, however, in order to establish that ACh plays some part in the initiation of the impulse, is to show that DFP blocks the conduction of the action potential because it gives rise to signs of persistent activity such as a reduction in the resting potential. Such an effect is produced by potassium, though the two actions do not run parallel (Steinbach, 1944). Recent work by Toman and others (1947) has made it clear that potassium and DFP can both block conduction, but that they do so by totally different mechanisms. When frog sciatic nerve is exposed to increased concentration of potassium, the action potential is abolished when the resting potential has been reduced by 20 to 30 per cent. In the early stages of this process the threshold to stimulation is reduced and the conduction rate is increased. The action of DFP, however, is to maintain the resting potential or increase it slightly, to reduce the conduction rate, and to increase the threshold. It has been known for some time that the local anæsthetics also block conduction in nerve fibres while maintaining the resting potential. Lorente de No (1944) showed that ACh and eserine up to a concentration of 0·001M did not block conduction but maintained the resting potential. They shared with added magnesium the property of delaying the fall in resting potential produced by asphyxia of the nerve. Eserine, in concentration of 0·01 M or over, blocked conduction, but also decreased the resting potential. If, however, blocking of conduction and inhibition of cholinesterase can occur with DFP but without change in the resting potential, it is difficult to ascribe this effect of eserine to its anticholinesterase activity.

It is, however, pointed out by Steinbach (1944) that " the injury potential should be regarded as a measurable force (or quantity since some current must be flowing) which may reflect drastic weakening of the membrane . . . Rectification may be a better measure of conditions at the surface of a cell ; it in turn is probably considerably less sensitive than the action potential or impedance changes measured by Cole and his collaborators."

It has also been shown that although added potassium does decrease the membrane resistance of unmyelinated giant fibres, ACh has no such effect even in very high concentrations (Hodgkin, 1947). Most of the work on the effect of DFP on the blocking of the action potential has been carried out on these fibres (Bullock, Nachmansohn, and Rothenburg, 1946), and it seems clear that as far as these fibres are concerned Nachmansohn's view of ACh as an agent which increases membrane permeability is therefore not really tenable. The persistence of ACh seems to be associated with an increased stability of the cell membrane. There may be some important differences between giant fibres and frog sciatic nerve fibres, since the threshold of the former is increased by added potassium, (Hodgkin, 1947 ; Toman and others, 1947), whereas the threshold of frog sciatic nerve fibres seems to be lowered. No significant difference in the action of ACh or of DFP on these fibres has yet come to light.

ACh and Heart Muscle.—In spite of much conflicting evidence, it now seems clear that neither ACh nor vagal inhibitory impulses have any effect on the resting potential of heart muscle. This seems to be established for the frog's heart which has been arrested (Segers, 1945). With a slowly beating heart the effect of ACh is to reduce the refractory period (Drury and others, 1920), and to abolish the negative after-potential which follows each beat (Segers, 1945). If the heart is beating fast the negative after-potentials will sum, and the effect of suddenly arresting the heart by any means involving ACh or otherwise will be to produce an apparent positivity, the so-called Gaskell effect. The work of Eccles and Brown (1934) suggests that ACh produces a prolongation of the process of recovery of the pacemaker, a process unaccompanied by any detectable surface potential changes. There is, however, some evidence that ACh may depolarize an injured but incompletely depolarized point (Segers, 1945).

Saline Models.—Another argument for an effect of ACh in producing surface potential changes and in decreasing membrane resistance is derived from the work of Beutner and Barnes (1942) on models consisting of saline solutions separated by lipoid interfaces. It is not clear that these models have enough features in common with nerve cells to have any relevance to the present problem.

Artificial Synapses.—The position of a purely

" electrical " theory of junctional transmission has been strengthened by the discovery and analysis of a number of artificial synapses, in which an impulse from one nerve cell can excite a second in the absence of any specialized chemical transmitter mechanisms. The first of such systems to be discovered was that of Jasper and Monnier (1938), but as their synaptic delay was about 20 msecs. the processes involved were probably complex. Katz and Schmitt (1939) showed that an impulse in an unmyelinated giant fibre could cause a reduction in the threshold of an adjacent parallel fibre of about 20 per cent., and that this change in threshold was related to local current flow set up in the second fibre by the impulse in the first. This change was insufficient to excite, but by arranging the fibres so that the impulse never receded from the area of contact, and by making the fibres hyperexcitable by soaking in citrate, Arvanitaki (1942) was able to make the impulse in the first fibre set up an impulse in the second. Subsequently it was found that an artificial synapse could be set up between motor and sensory fibres at the cut surface of a mammalian nerve trunk (Granit and others, 1943). A similar effect whereby impulses could be synchronized was described much earlier by Adrian (1930) at the cut end of a mammalian nerve trunk *in vitro*. A theoretical treatment of the relation between anatomical arrangement and changes in current flow has been given by Eccles (1946b).

The concept of excitation by local circuits has been extended to the activation of cells in the central nervous system by electrical fields due to synchronous activity of large numbers of cells. The evidence for this phenomenon is very strong in the case of the frog's brain in which the synapses are poisoned with nicotine (Libet and Gerard, 1939). If now large slow electrical waves are set up by treatment with caffeine, not only can these waves spread across the whole of the cerebrum, but they can also cross a clean section of the brain, if the severed surfaces be again placed in apposition. Similar synchronization of large slow waves across a cut surface can occur when the spinal cord is strychninized, a few segments are cleanly divided, and the cut surfaces are put back into apposition (Bremer, 1941). For our present purposes we are merely concerned to establish that synchronous activation of nerve cells may occur by electrical means, in the absence of specific synaptic mechanisms.

Junctional Potentials.—Other far-reaching results of investigation of the electrical changes and the corresponding changes in the excitability of tissues have been the discovery of junctional potentials, of the end-plate potential of striated muscle, of the synaptic potentials of sympathetic ganglia (Eccles and Kuffler, 1941) and of motoneurones of the spinal cord (Brooks and Eccles, 1947). These junctional potentials are localized but spread decrementally ; they have a rapid rising phase and an exponential decay, with a total duration of from twenty to fifty times the duration of the action potential in the afferent fibre. They seem to give rise to impulses in the muscle fibre and the nerve cell during their rising phase, but throughout their course they also exert a facilitatory effect on the cell. In the nerve muscle junction, the end-plate potential is believed to behave in all respects like a brief cathodal polarization (Eccles and Kuffler, 1941). Assuming that the end-plate has similar properties to the nerve membrane it is possible to obtain some estimate of the time course of the transmitter agent responsible for this cathodal polarization, using Hill's (1936) equations for nerve. The transmitter agent, which may well be ACh, has an initial brief " spike " and a prolonged " tail." The spike is unaffected by anticholinesterases, but the tail is greatly increased. Although there is some evidence that the muscle fibre may accommodate to the presence of the end-plate potential, it may be large enough in the presence of anticholinesterases to give rise to repetitive responses of the muscle fibre. All the evidence is consistent with the view that the end-plate potential is an essential intermediary in the transmission from nerve to muscle.

Sympathetic Ganglia.—The situation in the sympathetic ganglia is in many points similar to that at the nerve muscle junction. A preganglionic volley can set up a synaptic potential which can be shown to precede the setting up of postganglionic impulses in the partially curarized ganglion. The synaptic potential seems to be due to a transmitter agent which is likewise removed by fast and slow processes, only the second of which is delayed by anticholinesterases. There is, however, still some doubt about the process responsible for the early part of the synaptic potential, a doubt which has been reinforced by recent work of de Castro (1942). He has taken the vagus nerve, and cut it above the nodose ganglion. Its central end, which after degeneration contains only sensory fibres, is then anastomosed to the lower end of the superior cervical ganglion. Contrary to expectations based on interpretations by Dale of the work of Langley and Anderson (1904), in 30 per cent. of cases the vagal sensory fibres which, like all other sensory fibres, are presumed to contain no ACh, yet succeed in establishing functional connexion with the ganglion cells. De Castro has shown that the addition of eserine does not in any way modify transmission across this ganglion. This is in striking contrast with the effects of eserine in the normal ganglion, in which eserine produces a considerable after-discharge

to a preganglionic tetanus. If, however, the cholinergic centrifugal fibres from the lower end of the nodose ganglion are anastomosed with the superior cervical ganglion, these junctions give an after-discharge on treatment with eserine. If these findings are to be relied upon, and it has been pointed out that fibres of unexpected origin frequently appear in degenerating nerve trunks, there are two far-reaching implications ; firstly that the rule that only cholinergic fibres can replace cholinergic fibres is not of general application, and secondly, and much more important, that there may be an excitatory effect common to all nerve fibres irrespective of their chemical affiliations.

The Central Nervous System.—In the central nervous system the important advances of the last ten years have been due to the analysis of the so-called " simple reflex " by limiting the stimulus used to fibres of the same function, instead of the blunderbuss stimulation of whole nerve trunks, and also to the study of the behaviour of as few neurones as possible by micro-electrode methods. In these ways it has been possible to separate two-neurone from multi-neurone reflex arcs and to distinguish between their properties. Just as central reflex time has had to be split into *nuclear delay*, the time needed to excite an internuncial pool, and *synaptic delay* proper, the time needed to excite the motoneurone (Lloyd, 1944), so it is necessary to distinguish between the components of central excitatory state due to internuncial reverberation and repetitive activity, and the residual facilitation which can be detected on motoneurones in a two-neurone arc (Lloyd, 1946 ; Eccles, 1946a). Central inhibitory state also seems to consist of a direct inhibition exerted on motoneurones, without measurable latency and reaching its maximum in 1 msec. (Lloyd, 1941) and much longer lasting processes occurring in interneurones probably due in part to the summation of subnormality (Lorente de No, 1939).

In order to obtain a volley of impulses in fibres of the same function, Lloyd (1946) used very weak stimuli applied to afferent nerve trunks from muscle, and recorded from the corresponding anterior roots. Such stimuli which will only excite the large proprioceptive fibres have been shown to produce a brief " residual facilitation " of motoneurones with an extreme duration of 10 or 15 msecs. The failure of Lorente de No (1939) to observe the phenomenon was probably due to the stimulation of mixed inhibitory and excitatory fibres by shocks applied to the posterior longitudinal bundle. Brooks and Eccles (1947a) have put forward a view of direct inhibition which is essentially similar to the decrease in excitability due to anodal polarization seen at an artificial synapse ahead of the advancing impulse (Katz and Schmitt, 1939). They suggest that Golgi cells with short axons may produce such an effect as long as excitation of the soma does not give rise to an impulse in its axon.

The Synaptic Potentials of Motoneurones.—Observations of the activity of motoneurones with micro-electrodes have confirmed and extended earlier observations on the potentials conducted decrementally down the anterior roots (Barron and Matthews, 1938). The synaptic potential begins about 0·3 msecs. after the arrival of the impulses at the motoneurone, reaches its peak after 1 msec., and decays over the next 10 msecs. The increase in the excitability of the motoneurone begins a little before the first sign of the synaptic potential, and rises very rapidly so that impulses are set up during its rising phase. The fall in synaptic potential goes parallel to the period of residual facilitation, and Eccles suggests that the synaptic potential is the electrical sign of the central excitatory state. The parallelism between the course of the summation of two synaptic potentials with the resulting outbursts of facilitated impulses as observed by Eccles (1946a) and the diagram of the presumed time course of the central excitatory state from the shortening of the central delay of the flexor reflex (Eccles and Sherrington, 1931) is particularly striking.

Any particular reflex usually makes use of pathways of various degrees of complexity. The knee jerk utilizes primarily two neurone pathways, but the after-discharge—which may be conspicuous in the toad, for example—is due to internuncial activity. The flexor reflex is mediated entirely by multi-neurone paths when unfacilitated ; but, when preceded by a facilitatory volley, its central delay is reduced to about 1·0 msecs., perhaps because three neurone paths are now able to excite the motoneurones.

Action of ACh and Anticholinesterases on the Central Nervous System.—When we turn to a survey of our present state of knowledge of the action of ACh and anticholinesterases on the central nervous system it is at once obvious that these analytical methods have not yet been fully applied. While all the recent advances in neurophysiology have been due to the precise delimitation of the unit activities studied, work on these drugs has been based on their effects on " simple reflexes " with techniques that are not capable of analysing the results in temporal, spatial, or functional terms.

The most notable exception is the work of Bremer (1937), who pointed out that the effect of 0·1 μg. ACh injected intra-arterially in his preparation of the *encéphalé isole* was exerted solely on the after-discharge to a sensory stimulus, not at all on the

primary wave. This contrasts with the effect of strychnine, which amplifies the primary wave and depresses the after-discharge. Nembutal has a selective depressant effect on the after-discharge. Exactly similar phenomena were observed in the spinal reflexes of the toad, in which after-discharge is conspicuous and long-lasting. The after-discharge was greatly increased by 0·25 μg. ACh injected intra-arterially, with little change in the primary reflex discharge. The anticholinesterases had similar selective effects (Bremer and others, 1942). Few comparable data are available for mammalian spinal reflexes, since most observations have been made with mechanical myographs of low natural period which are incapable of recording separately the much briefer initial reflex responses and after-discharges. When electrical recording methods have been used, they have recorded the summed electrical activity of a muscle and do not usually permit the observation of the evolution of the discharge in a single motor unit. The observations of Wikler (1945), however, have been made with a technique similar to that of Lloyd. He finds that eserine (0·25 mg/kg) does augment two neurone arcs in the spinal cord of the cat.

Some interesting conclusions may be drawn from the mechanical records available. Those of Bülbring and Burn (1941) have the great advantage that they were made on dogs with the spinal cord separately perfused from the muscles used for recording, so that no doubt the effects concerned were central and not peripheral. They found that ACh injected intra-arterially in doses of 1 μg, produced contractions of muscles after a latency of 10 to 20 seconds. ACh without an anticholinesterase slightly augmented the flexor reflex, but had a slight transient depressant effect on the knee jerk. This difference was accentuated by anticholinesterases which depressed the knee jerk and augmented the flexor reflex. Rebound after inhibition of the knee jerk was greatly augmented by eserine. Calma and Wright (1944), have examined the effect of eserine by intrathecal injection on decerebrate and chloralosed cats. They occasionally find selective effects on the first recorded contraction and the after-waves, especially with small doses. When they obtain very large increases in tone of the quadriceps there is a fall in the peak tension of the knee jerk. This must represent a very large decrease in the excitability of the reflex centres to the afferent volley, since the knee jerk normally increases rapidly in size with increase of the initial tension in the muscle, owing to the excitation of additional stretch receptors. Up to four-fold increases in the height of the knee jerk were recorded in experiments in which the tension of the resting muscles apparently did not change much. They also find the crossed extensor and jar reflexes are increased by eserine, but the effect on the flexor reflex is variable. Inhibitory phenomena are not uncommon. Kremer (1942) obtained evidence of inhibition of the knee jerk and of spasticity in man following on the intrathecal injection of prostigmine and eserine. These results have recently been confirmed by Guttmann (1948) on patients with complete spinal transsections. He finds that spasticity is abolished by prostigmine, as is the reflex emptying of the bladder, but the spinal vasomotor reflexes persist and, in a high proportion of patients, ejaculation takes place.

Selective Effects.—Crucial evidence for a selective effect on two-neurone and multi-neurone pathways can only come from preparations in which the motoneurones are not depressed by anæsthetics or narcotics, and are not subjected to an increased facilitatory bombardment from other parts of the cord. Such evidence is provided by Eccles (1947), who has observed the effects of ACh on the synaptic potential and on impulse discharge in the spinal cord. In the deeply anæsthetized cord he finds no effect whatever of ACh. In the unanæsthetized cord ACh has either no effect on the rising phase of the synaptic potential or it may cause a small decrease attributed to occlusion. The falling phase is obscured by irregular activity due to internuncial discharge, which begins after about 3 or 4 msecs. Eccles (1947) also points out that in the nerve muscle junction large amounts of ACh block the transmission of impulses and abolish the end-plate potential. A similar blocking of impulses and diminution of the synaptic potential can be demonstrated in the superior cervical ganglion. No such effect is demonstrable in the spinal cord. Even in the presence of very large amounts of ACh with an anticholinesterase, in the anæsthetized cord the synaptic potential is unaffected, and in the unanæsthetized cord it shows only a slight diminution. Unlike the junctional potentials in the nerve muscle junction and the ganglion, the synaptic potential of the cord is not prolonged by the action of anticholinesterases.

On the other hand, in view of the presence of preformed ACh, cholinesterase, and choline acetylase in the central nervous system, it is a little difficult to dismiss the excitatory effects of less than 1 μg. ACh as pharmacological actions. As there is some evidence for an action of ACh on recovery processes in the peripheral nerve, the possibility of a similar action on central neurones seems worth exploring.

Repetitive Activity.—There is good evidence of a selective effect of ACh on repetitive activity, particularly on internuncial cells. The evidence of Eccles (1947), Bremer (1937), Bremer, Bonnet, and Moldaver

(1942) strongly supports this view, and the work of Calma and Wright (1946) is consistent with it. It is unfortunate that the effect of close arterial injection of ACh was not observed in the elegant experiments of Wikler (1945).

If this facilitatory effect of ACh on repetitive activity be admitted, some idea of its mechanism seems to be necessary. It has been suggested by Lorente de No and Feng (1946) that a decrease in the L fraction of the membrane potential, which is normally responsible for a large fraction of the negative after-potential, is a necessary condition for the appearance of rhythmic activity in frog nerve. It has been shown that the negative after-potentials of cardiac muscle are reduced by ACh, and that DFP has some similar effect on frog sciatic nerve. In more general terms, however, the persistence of ACh seems to lead to a stabilization of the cell membrane. If it be true that rhythmically active cells of the spinal cord are likely to outrun their blood supply, as seems to be true of the cells of the cerebral cortex (Davis, McCulloch, and Roseman, 1944), then it is possible that the presence of ACh would increase the rate of recovery and increase the maximum rate at which the cell could discharge. This view would fit with the observations of Welsh and Hyde (1944), who find that the richness in ACh in various parts of the rat's brain varies with the resistance to asphyxia.

Excitatory and Paralytic Effects of Anticholinesterases.—A possible analogy for the reversal of effects with size of dose which occurs in the action of anticholinesterases on the central nervous system is provided by the so-called paralytic effect of overdose of prostigmin on the nerve muscle junction. Small doses of prostigmin increase the muscular contraction to a single volley by producing repetitive discharge. Large doses paralyze the muscle by allowing the accumulation of such large amounts of ACh that the end-plate remains permanently depolarized. In tissues which are not depolarized by ACh, some other explanation must be sought. If one regards the rhythmically active cell as a simple relaxation oscillator, it is clear that rhythmic activity can be abolished when the cell is permanently in either of its stable states, that is, for a nerve cell, when it is permanently polarized or depolarized. It is possible that acceleration of recovery processes might lead to the excessive stability of the cell membrane, with a resulting inexcitability. In this way ACh or an anticholinesterase might lead to increased internuncial activity in small doses, but might abolish activity in large doses.

Other complications are not lacking. It has been shown unequivocally that in giant nerve fibres eserine can penetrate the cell membrane and inhibit cholinesterase, whereas prostigmin cannot (Bullock, Nachmansohn, and Rothenburg, 1946). It was suggested by Schweitzer, Stedman, and Wright (1939) that the water and lipoid solubility of tertiary and quaternary ammonium compounds with anticholinesterase activity might determine whether the substance had an excitatory or depressant effect. There seems now to be no reason why these hypotheses should not be tested on unitary activities under more rigid conditions.

Observations of the effect of these drugs on the cortex have been complicated by the unsuspected existence of a cholinergic vasomotor system activated by nerve fibres from the greater superficial petrosal nerve (Darrow and others, 1944). It is therefore possible that some of the effects of cholinergic drugs on the cortex may have been due to vasodilatation with an increased blood flow, with a resulting increase in the local *p*H and an increased local excitability of cortical neurones (Dusser de Barenne and others, 1937).

Electrical and Chemical Aspects of Synaptic Transmission.—At one time attempts were made to harmonize electrical and chemical aspects of synaptic transmission by pointing out that all current flowing in living tissues must be carried by ions, and that acetylcholine might be ionized in solution and have peculiar properties in moving from watery solutions into lipoid layers under the influence of potential gradients. No measurements of its ionic mobility have yet been made, and measurements under relevant conditions would be very difficult to make. Its limited effects on the electrical behaviour of nerve have not given much encouragement to this view, but it is by no means ruled out. It has not been suggested that adrenaline owes its excitatory effects to any electrical properties it may have, but it does show a variety of curious interactions with acetylcholine (Burn, 1945). Adrenaline is known to increase the negative after-potential in the heart, (Segers, 1945), and it is possible that these interactions between ACh and adrenaline take place at the point at which energy is made available by the enzyme systems for the rebuilding of the cell membrane. Recent work on the synthesis of ACh has established that it is related to adenosine triphosphate, to creatine phosphate, and, in fact, to the main lines of intracellular enzyme organization (Feldberg, 1945; Nachmansohn, 1945).

Summary

1. The evidence for the mode of action of acetylcholine on nerve and muscle suggests that, although it produces depolarization at the nerve muscle junction, it does not do so on nerve or on heart muscle.

Its first effect on heart muscle is to reduce the negative after-potential, and to reduce the refractory period.

2. Recent advances in neurophysiology have depended on the analysis of the so-called simple reflex by means of the stimulation of units of uniform function, by recording from as few units as possible and by the accurate analysis of events in time. These methods have as yet hardly been applied to the study of the effects of ACh and anticholinesterases on the central nervous system.

3. The data at present available suggest that the excitation of a motoneurone is due to the cathodal polarizing effect of the synaptic potential set up by the afferent volley. ACh seems to have no effect on this process. The main action of ACh in the central nervous system seems to be the facilitation of repetitive activity, particularly in interneurones. The mode of production of this internuncial facilitation is at present a subject for speculation.

References

Adrian, E. D. (1930). *Proc. roy. Soc.*, **106B**, 596.
Arvanitaki, A. (1942). *J. Neurophysiol.*, **5**, 89.
Barron, D. H., and Matthews, B. H. C. (1938). *J. Physiol.*, **92**, 276.
Beutner, R., and Barnes, T. C. (1942). *Science*, **94**, 211.
Bremer, F. (1937). "L'Activité Electrique de l'Ecorce Cérébrale." Hermann. Paris.
——(1941). *Arch. internat. Physiol.*, **51**, 211.
——, Bonnet, V., and Moldaver, J. (1942). *Ibid.*, **52**, 215.
Brooks, C. McC., and Eccles, J. C. (1947a). *Nature, Lond.*, **159**, 760.
——, and —— (1947b). *J. Neurophysiol.*, **10**, 251.
Bulbring, E., and Burn, J. H. (1941). *J. Physiol.*, **100**, 336.
Bullock, T. H., Grundfest, H., Nachmansohn, D., Rothenburg, M. A., and Sterling, K. (1946). *J. Neurophysiol.*, **9**, 253.
——, Nachmansohn, D., and Rothenburg, M. A. (1946). *Ibid.*, **9**, 9.
Burn, J. H. (1945). *Physiol. Rev.*, **25**, 377.
Calma, I., and Wright, S. (1944). *J. Physiol.*, **103**, 93.
——, and —— (1946). *Ibid.*, **106**, 80.
Cole, K. S., and Curtis, H. J. (1939). *J. gen. Physiol.*, **22**, 649.
Cowan, S. L. (1938). *J. Physiol.*, **88**, 3P.
Darrow, C. W., Green, J. R., Davis, E. W., and Garol, H. W. (1944). *J. Neurophysiol.*, **7**, 217.
Davis, E. W., McCulloch, W. S., and Roseman, E. (1944). *Amer. J. Psychiat.*, **100**, 825.
de Castro, F. (1942). *Trab. inst. invest. biol. Madrid.*, **34**, 217.
Drury, A. N., Lewis, T., and Bulger, A. H. (1920). *J. Physiol.*, **54**, 97P.
Dusser de Barenne, J. G., McCulloch, W. S., and Nims, L. (1937). *J. cell. comp. physiol.*, **10**, 277.
Eccles, J. C., (1942). *J. Physiol.*, **101**, 465.
—— (1944). *Ibid.*, **103**, 27.
—— (1946a). *J. Neurophysiol.*, **9**, 87.
—— (1946b). *Ann. N. Y. Acad. Sci.*, **47**, 429.
—— (1947). *J. Neurophysiol.*, **10**, 197.
——, and Brown, G. L. (1934). *J. Physiol.*, **82**, 242.
——, and Kuffler, S. W. (1941). *J. Neurophysiol.*, **4**, 486.
——, and Sherrington, C. S. (1931). *Proc. roy. Soc.*, **107B**, 511.
Feldberg, W. (1945). *Physiol. Rev.*, **25**, 596.
Gerard, R. W. (1946). *Ann. N. Y. Acad. Sci.*, **47**, 575.
Granit, R., Leksell, L., and Skoglund, C. R. (1944). *Brain*, **67**, 125.
Guttmann, L. (1948). In the press.
Hill, A. V. (1936). *Proc. roy. Soc.*, **119B**, 305.
Hodgkin, A. L. (1939). *J. Physiol.*, **94**, 560.
——(1947). *Ibid.*, **106**, 319.
Jasper, H. H., and Monnier, A. M. (1938). *J. cell. comp. physiol.*, **11**, 259.
Katz, B., and Schmitt, O. H. (1939). *J. Physiol.*, **97**, 471.
Kremer, M. (1942). *Quart. J. exp. Physiol.*, **31**, 337.
Kuffler, S. W. (1943). *J. Neurophysiol.*, **6**, 99.
Langley, J. N., and Anderson, H. K. (1904). *J. Physiol.*, **31**, 365.
Libet, B., and Gerard, R. W. (1939). *J. Neurophysiol.*, **2**, 153.
Lloyd, D. P. C. (1941). *Ibid.*, **4**, 184.
——(1944). *Physiol. Rev.*, **24**, 1.
——(1946). *J. Neurophysiol.*, **9**, 421.
Lorente de No, R. (1939). *Ibid.*, **2**, 402.
——(1944). *J. cell. comp. physiol.*, **24**, 85.
——,and Feng, T. P. (1946). *Ibid.*, **28**, 397.
Nachmansohn, D. (1945). *Vitamins and Hormones*, **3**, 337.
——(1946). *Ann. N.Y. Acad. Sci.*, **47**, 395.
Osterhout, W. J. V., and Hill, S. E. (1930). *J. gen. Physiol.*, **13**, 547.
Renshaw, B. (1940). *J. Neurophysiol.*, **3**, 373.
Schweitzer, A., Stedman, E., and Wright, S. (1939). *J. Physiol.*, **96**, 302.
Segers, M. (1941). *Acad. roy. Belge, Memoirs*, **1**, fasc., 7, 1.
——(1945). *Arch. int. Pharmacodyn.*, **71**, 173.
Steinbach, H. B. (1944). *J. cell. comp. physiol.*, **24**, 291.
Toman, J. E. P., Woodbury, J. W., and Woodbury, L. A. (1947). *J. Neurophysiol.*, **10**, 429.
Welsh, J. H., and Hyde, J. E. (1944). *Ibid.*, **7**, 41.
Wikler, A. (1945). *Proc. Soc. exp. biol. N.Y.*, **58**, 193.

BOOK REVIEWS

A TEXTBOOK OF MENTAL DEFICIENCY

A. F. Tredgold

(London. Bailliere, Tindall, and Cox. Seventh Edition. Pp. xvi+534, with 47 plates. Price 30*s.* net.)

No aspect of medicine better supports the view of " busy common sense " that brain is the organ of mind than does the study of mental deficiency ; and it is a subject of growing interest to both neurologists and psychiatrists. For the neurologist, the renewed enquiries into cortical cyto-architecture that Lashley and his colleagues have begun will ultimately establish a more clear-cut picture of normal cortical histology against which the ament brain will also have to be re-assessed ; and application of the more searching psychometric tests which have become available in the last few decades may well provide an advance in the correlation of brain structure and function. For the psychiatrist, the importance of the constitutional factor in the ætiology of mental disease which is once more being emphasized, is even more firmly underlined and more readily studied in mental deficiency practice. From the latest edition of Dr. Tredgold's *Mental Deficiency* it would seem that the material for such practice is on the increase. Yet it is an unhappy fact that the Mental Deficiency Acts of 1913 and 1927 are still to a large extent rendered nugatory by the lack of adequate buildings and staff to deal with defectives.

This new edition of a well-established work remains a thorough and well-balanced introduction to the subject, and when the author argues for views which are not generally accepted he makes it clear in the text. Thus, on the subject of ætiology he still supports the hypothesis of germ corruption, though it is difficult at times to see in his arguments any necessary differentiation between this and the more generally accepted theory of specific gene abnormality. For permutation and combination of individual genes allows of almost limitless variation and gradation in the phenotype.

The section on psychology is essentially an eclectic and common-sense one, and no attempt is made to discuss the mental mechanisms of aments in terms of Freudian or Meyerian psycho-pathology.

The discussion on pathology is as full as it can be, but reflects the general paucity of information on the range of normal of both histological and biochemical aspects of brain.

The clinical descriptions and varieties of primary amentia are detailed, clear-cut, and memorable. Mongolism is included in the primary group, and few would disagree with this. The ætiology of this condition is discussed at some length. It is understandable that the causes of such a well-defined clinical syndrome should be of special interest, but it may be doubted whether F. G. Crookshank's ætiologica! " jeu d'esprit " deserves even the small amount of discussion it gets. The group of secondary amentias is also fully treated. On the relationship between epilepsy and amentia the author holds the view that there is an amentia which is induced by epilepsy. There is, however, little unequivocal evidence in support of this, for even when epilepsy precedes the amentia the two may still be unconnected, the latter being genetically determined but of late onset as in the dementia of Huntingdon's chorea.

In the description of mental tests space perhaps might have been found for mention of the " factorial " approach of the Spearman school, for such an approach may well find an application in the investigation of the " idiots savants " so interestingly reviewed in a separate chapter.

In a very full discussion of the problem of moral defectives the author appears to agree with the widespread view that in most cases the lack of " wisdom " or " common sense " shown by these persons is of such a nature as to suggest intellectual defect, even though this is not demonstrable by intelligence tests.

The vexed question of the McNaughten Rules is once again brought up, and the author argues cogently for their revision. Most doctors and a growing body of lawyers are with him in this.

Finally Dr. Tredgold puts forward decided views on the eugenic aspect of mental deficiency. Ever since the first edition of his book in 1908 he has championed the need for limiting the propagation of this stock. However much we agree or disagree with his view, the sociological implications of the facts he brings forward must be a matter of concern to every thoughtful citizen.

Dr. Tredgold has seen the issue of seven editions of his work over a period of nearly 40 years, and for many years now it has been recognized both here and in the U.S.A. as one of the standard introductory works on the subject. The present edition ensures that it will maintain this high position.

PSYCHIATRIC RESEARCH

By C. K. Drinker and others

(Cambridge, Mass. Harvard University Press. London : Geoffrey Cumberlege. 1947. pp. 113. Illustrations and diagrams. Price $2 or 11*s.* 6*d.*)

This is a collection of six addresses delivered at the McLean Hospital, Massachusetts, on the opening of a laboratory for biochemical research in psychiatry. As might be expected, the approach to the main theme differs very much from one address to another. Only two deal solely with specific psychiatric problems : these are the contributions of Wilder Penfield on

"Psychical Seizures," and of Jordi Folch on "Biochemical Problems related to Psychiatry." The subject of the first of these—the psychomotor variants of the epileptic seizure—lies on the indeterminate boundary that divides neurology from psychiatry. Penfield correlates the clinical characteristics of the seizures with cortical areas and electro-encephalographic findings. The second paper, by Folch, is a survey of recent research on the chemistry of the brain. Of the six papers, it is the one of greatest scientific interest and is followed by sixty-five references to the growing literature of this subject. Dr. Folch is to be the director of the new laboratory.

Stanley Cobb, in "Integration of Medical and Psychiatric Problems," describes the work done in the psychiatric ward of the Massachusetts General Hospital since 1934; the latter half of his paper deals with the researches into neurocirculatory asthenia carried out in his department during that period.

The remaining three papers are discussions of psychiatric research in more general terms. Drinker's contribution is an historical survey of the development of the department from the original McLean Asylum, founded in 1818 under the directorship of Dr. Rufus Wyman. Strecker, in "The Psychobiology of Psychiatric Research," issues a warning against the all-too-common tendency to diagnose and treat mental illness on the basis of a single cause, and he pleads for a corresponding breadth of vision in approaching problems of research. In the remaining paper, "Protocol for a Review of Psychiatry," Gasser discusses in general the evolution of the scientific method and ends his address with a graceful tribute to the research already done at the McLean Hospital.

NEOCORTEX OF MACACA MULATTA

G. von Bonin and P. Bailey

(University of Illinois Press. 1947. Pp. 163; Illustrated. $4.00 paper bound, $5.00 cloth bound.)

Illinois Monographs in the Medical Sciences, Vol. 5, No. 4.

Neurophysiologists have in recent years become increasingly concerned regarding the inaccuracies contained in the widely accepted cytoarchitectural descriptions of the mammalial cortex. The authors of this study have therefore made a determined effort to describe and illustrate (with the aid of 62 plates) the structure of the various cortical regions in the Macaque monkey. Neurologists will be disappointed to read that they have found the well-known Brodmann's numerical system to be so inaccurate that they have felt obliged with reluctance to abandon his method in favour of Economo's symbols. The authors are impressed with the similarity in cortical organization between the macaque and man, and emphasize the evidence that the structural pattern of cortical organization is essentially the same in all primates and perhaps in all mammals. Hence the importance of a study such as this, and many will feel indebted to the authors for clarifying a difficult subject.

THE TREATMENT OF PURULENT PACHYMENINGITIS AND SUBDURAL SUPPURATION WITH SPECIAL REFERENCE TO PENICILLIN

BY

F. SCHILLER, H. CAIRNS, and DOROTHY S. RUSSELL

From the Radcliffe Infirmary, Oxford

(RECEIVED MAY 3, 1948)

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Introduction

In this paper we report four years' experience of penicillin in the treatment of purulent pachymeningitis. Formerly, even after the introduction of sulphonamides, the condition was almost always fatal; since the advent of penicillin seven of our fifteen cases have recovered, and these results should be greatly bettered now that penicillin is freely available and we are beginning to understand the problems of treatment. Excluding cases in which the condition was secondary to cerebral lesions, we have seen in all thirty-three cases of this disease in the last twenty years (Table I).

Purulent pachymeningitis is characterized by a film of pus of variable thickness in the subdural space spreading over part or whole of one or both cerebral hemispheres. It has been termed subdural empyema, subdural abscess, internal purulent pachymeningitis, and various other names. We prefer the term purulent pachymeningitis on analogy with the term purulent peritonitis. As in peritonitis, the pus tends at first to spread diffusely, but then may become closed off in a number of loculated subdural abscesses. As in purulent peritonitis so in purulent pachymeningitis, drainage of the pus at one part of the subdural space in the acute stage may not always prevent its loculation at another part of the subdural space at a later stage. A favourite site of loculation in the peritoneal cavity is in the space between the diaphragm and liver, which is as narrow as the subdural space. In another flat space lined with endothelial cells, the pleural cavity, loculation of pus is also apt to follow generalized suppuration.

Purulent pachymeningitis is usually secondary to

TABLE I

PURULENT PACHYMENINGITIS: SITE OF PRIMARY INFECTION AND DISTRIBUTION OF ORGANISMS

Primary infection	Strep.	Strep. and Staph.	Staph.	Pneum.	No record or inconclusive	Total
Paranasal sinus	18	—	—	1	4	23
Mastoid	3	1	—	—	2	6
Distant focus	3	—	1	—	—	4*
Total	24	1	1	1	6	33

* Distant foci were situated as follows: subcutaneous, 2; peritoneal cavity, 1; tooth and pleural cavity, 1.

TABLE II

PASSAGE OF PENICILLIN FROM BLOOD TO SUBDURAL FLUID IN TWO CASES OF SUBDURAL HÆMATOMA

Minutes after intramuscular injection, 200,000 units	Penicillin in subdural fluid units per c.cm.	
	Case 1	Case 2
0	0	0
2	0	—
10	—	0·3
20	0·5	—
22	0·05*	—
30	—	0·4
35	—	0·15*
50	—	0·05*

* Subdural fluid diluted with Ringer's solution.

spreading osteomyelitis of the skull, which is an unhappy sequel in some cases of pansinusitis (Plate I a) and mastoid disease, and otologists have written extensively on the subject (McKenzie, 1913). There has been some confusion about the situation in which the intracranial pus collects. Some of the earlier writers called any collection of pus inside the dura a cerebral abscess, but from their descriptions it is clear that some at least of these were subdural (McKenzie, 1913). The differences between leptomeningitis and pachymeningitis have not always been clearly understood, and pus which is obviously subdural pus of pachymeningitis has been described as "in the subarachnoid space between both hemispheres" (Mair, quoted by Dreyfuss, 1896) or in the "cavum arachniodeum" (Paulsen, quoted by Dreyfuss, 1896). Pus encountered when the dura is opened is usually subdural and not subarachnoid.

The subdural and subarachnoid spaces are quite distinct.* The subdural space usually appears to be empty, but Penfield (1924) showed that in dogs it may contain small amounts of clear yellow fluid. It is bounded by dura without and arachnoid within, is lined with a single layer of endothelial cells, and is a single continuous space over the surface of the brain and spinal cord, except where arachnoid granulations are embedded in the dura. Air passes readily from one end of the cranial subdural space to the other (Plate I b and c). Penicillin passes readily to and fro between the blood stream and any fluids which may accumulate in the subdural space (Table II). The subarachnoid space, on the other hand, is a channel traversed by numerous fine septa and containing cerebrospinal fluid. Air in it cannot move freely with alterations of head posture, (Plate II d and e); and penicillin does not pass freely between the blood and cerebrospinal fluid. The arachnoid membrane is a firm barrier between the subdural space and the cerebrospinal pathways, only weakened by the fact that it is pierced by entering and leaving blood vessels, and by the arachnoid granulations which burrow into the dura mater. With these facts in mind it is easy to understand that pus may spread widely in the subdural space without any gross signs of ieptomeningitis.

There are several varieties of subdural suppuration, but in this paper we are concerned only with purulent pachymeningitis and those subdural abscesses which are formed when the subdural pus becomes loculated. The reason for so narrowing our attention is that purulent pachymeningitis is a distinct pathological entity which produces a sharply defined clinical picture, and, now that it can be treated successfully, it is important that this should be recognized. Infections of the subdural space are often complicated by infections in other parts of the cranial chamber, and the chain of pathological events in any one case may baffle the clinician. In the cases which we describe the intracranial infection always began with purulent pachymeningitis which could be recognized clinically even though in some cases it was soon alleviated by penicillin, or otherwise modified by the formation of a loculated subdural abscess, with or without a cerebral abscess. Hence we exclude the following types of subdural suppuration.

1. Localized subdural abscess secondary to, or arising simultaneously with, a subjacent cerebral abscess.

2. Localized subdural abscess following focal necrosis of the dura, as a sequel to focal osteomyelitis of the petrous or other bones of the skull.

The distinction of these conditions from purulent pachymeningitis is not always possible clinically, especially now that penicillin is proving effective in controlling the spreading type of infection, but nevertheless it should be drawn whenever possible because of its therapeutic importance. In localized subdural abscess intracranial surgical treatment can be limited to the area of the abscess. In purulent pachymeningitis, on the other hand, penicillin instillations of the whole subdural space are often necessary if loculation of pus alongside the falx cerebri is to be prevented.

3. Infected subdural hæmatoma. The common subdural hæmatoma of civilian practice may become infected after operation. Infected subdural hæmatoma may also occasionally arise after a radical ethmoid operation at which the overlying dura has been penetrated (Cairns, 1937, Case 10). This is a condition which may simulate purulent pachymeningitis.

* The subdural space is inconspicuous and is not recognized at all by some writers. Thus Logan Turner and Reynolds do not figure it in their diagram of the coverings of the brain (Turner and Reynolds, 1931, Fig. 1).

TABLE III

LESIONS ASSOCIATED WITH PURULENT PACHYMENINGITIS (THIRTY-THREE CASES)

	Total cases	Spreading osteo-myelitis of skull	Extradural abscess	Thrombo-phlebitis or sinus thrombosis	Cerebral abscess	Severe lepto-meningitis	Pulmonary abscess	Subdural loculation
Sinus infection	23	19	12	4	3	6	2	13
Mastoid infection	6	4	3	4	2	—	—	3
Distant focus	4	3	1	—	3	1	—	—
Total	33	26	16	8	8	7	2	16

4. Subdural suppuration, or infected subdural hæmatoma secondary to penetrating or non-penetrating missile wounds of the head. Three cases of this condition have recently been described (Cairns and others, 1947, Cases 1, 2, and 12) and it is of interest in connexion with the present study that the predominant organisms were non-β-hæmolytic streptococci—the same group of organisms, in fact, which cause the purulent pachymeningitis of civilian practice.

Pathology

At necropsy there are the lesions directly connected with the subdural suppuration, and the associated infective lesions (Table III) which vary from case to case. It will be convenient first to deal with purulent pachymeningitis and its effects, and later to consider the associated lesions.

PACHYMENINGITIS

At operation or necropsy in the acute stage the subdural space contains free pus which is limited to and more or less evenly distributed over part or whole of one or both cerebral convexities. Though usually thick and creamy, it is easily wiped away from the limiting membranes of the space, leaving smooth surfaces. The leptomeninges may be opaque and there may be, in places, an excess of subarachnoid fluid, but in uncomplicated cases purulent exudate is not present beneath the arachnoid. When the dura is opened at operation a small amount of pus escapes and then the brain, which is usually under raised pressure, plugs the dural opening. Further pus can be obtained by depressing the brain. At necropsy severe herniation of the uncinate gyri through the tentorial opening, or of the cerebellar tonsils through the foramen magnum, indicates the great rise of intracranial pressure.

At a later stage the pus becomes thicker, and fibrinous adhesions develop between the dura and arachnoid; the surfaces of the dura and arachnoid lose their normal lustre. There is a tendency, too, for the pus to concentrate at certain points, such as alongside the falx (Plate II a), or on the upper surface of the tentorium (Plate II b), or on the diaphragma sellæ. Such loculation leads, still later, to segregation of the pus into abscesses. There is then a corresponding deformity of the adjacent brain. A grey membrane of variable thickness forms on the deep aspect of the dura and, less marked, over the opposing arachnoid. Until it is organized this membrane is shaggy and friable. By organization it is converted into fibrous granulation tissue. The end results of the process will vary macroscopically according to the amount and distribution of the pus. In some areas, where the pus has not amounted to more than a thin film, the subdural space may resume its patency and the dura shows little change beyond a grey, or greyish-brown thickening of its innermost areolar layer. Elsewhere the dura is united to the arachnoid by an opaque yellow lamina of fat-granule cells and this is eventually organized by fibrous tissue, the dura thus becoming firmly fused to the arachnoid membrane. Greater accumulations of pus become loculated to form abscesses (Plate II b).

Microscopical Appearances

NORMAL HISTOLOGY OF THE DURA.—The cranial dura is composed of two stout layers of dense collagenous tissue, the fibres of the layers being collectively oblique to one another. In the mature meninx cells are scanty. The included blood vessels lie mainly along the junction of the two layers; elsewhere they are more frequent in the inner than in the outer layer. Elastic fibres are both delicate and scanty. Bounding the subdural space is an inner areolar layer, so thin as to be practically linear in vertical sections. This contains a few

capillaries and is limited by a flattened endothelium of polygonal cells (Weed, 1932), which, however, is not obvious in sections of human necropsy material.

Purulent Pachymeningitis

Early Stages.—Purulent pachymeningitis is a misnomer in that the dura remains remarkably free from infiltration by the leucocytes that collect in the subdural space, with the exception of areas contiguous to bone affected by purulent osteomyelitis. But its reactions, and those of the opposing leptomeninges, are characteristic and resemble those seen in subdural hæmatoma. They are, however, of a more vigorous character and determine the organization and segregation of the adjacent pus.

At an early stage proliferation of blood vessels and multiplication of large mononuclear macrophages begin in the inner layer of collagenous fibres, and in the boundary zone between this and the outer collagen layer. There is little alteration of the latter. The proliferating vessels and cells extend inwards to enter the fibrin and pus in the subdural space. First the large mononuclear cells are seen in small groups, in active phagocytosis, immediately beneath the dura. Later they are followed by capillaries. Fibroblasts then appear also, and lay down collagen fibres. By a progression of this sequence of changes from without inwards a layer of fibrous granulation tissue comes into being which is incorporated with the inner areolar layer of the dura and gradually encroaches on the pus.

Simultaneous changes occur in the leptomeninges. Provided that the infection does not extend into the subarachnoid spaces the inflammatory changes found in the latter are non-purulent. At the earliest stages the leptomeninges are distended by œdematous exudate containing abundant filaments of fibrin. Polymorphonuclear leucocytes are scanty, and are exceeded in number by large mononuclear cells (phagocytes) of arachnoid origin. These quickly multiply and become the predominant cell. The pia at first is little affected, but later there is a chronic type of inflammatory cellular infiltration characterized by plasma cells, lymphocytes, and large mononuclear cells.

As in subdural hæmatoma, so here too the leptomeninges provide a granulation tissue that organizes the subdural exudate from below. The reaction is slower and less vigorous than that which takes place from the dural side. Large mononuclear cells, however, migrate through the arachnoid membrane to invade the pus, and are followed later by capillaries and spindle fibroblasts, which lay down rather scanty collagen fibres.

Later stages are those of complete organization and gradual regression to a resting stage. Provided that complicating pathological conditions do not arise, the pus in the subdural space will ultimately be replaced by macrophages : the advancing ranks of cells from dura and arachnoid respectively meet and form a united layer. At this stage the dura and arachnoid are in close apposition, lightly adherent by a moderately firm opaque yellow film, which at first may be easily broken down manually but which soon becomes organized by collagen so that the brain is firmly united to the dura (Plate II a).

But this presupposes that the exudate amounts to no more than a thin layer. In places the accumulation of pus may be relatively great, and here it is found that organization is completed about the margins, where the pus is scantier, while the central collection forms an abscess. Certain of the localized subdural abscesses that occur in the course of a more diffuse infection of the subdural space are therefore simply areas where organization is delayed by the greater bulk of the exudate.

Where the exudate is minimal it may be completely removed with no greater residua than slight fibrous thickening of the innermost areolar layer of the dura, with perhaps a little perivascular lymphocytic infiltration.

With the development of organized tissue in the subdural space the dura reverts to its normal content of cells and blood vessels. The leptomeninges, on the other hand, undergo fibrous thickening and the chronic inflammatory cellular exudate in the pia persists for considerably longer periods.

Resolution after Treatment by Penicillin.—In one case in the present series it is possible to report the histological appearances, following successful treatment of suppurative pachymeningitis by irrigation of the subdural space with a penicillin solution. This patient died of a loculated right subdural abscess, and on the left side where the original purulent pachymeningitis had been encountered there was at necropsy no macroscopic abnormality other than diffuse orange staining of the inner aspect of the dura, and a few delicate adhesions between arachnoid and dura.

Microscopically the dura of this region showed the slight fibrous thickening of the inner areolar layer already described as the end result of complete resolution. A few pigment-macrophages, plasma cells, and lymphocytes were present in this layer. The leptomeninges had undergone slight fibrous thickening, both of arachnoid and pia, and contained a slight excess of perivascular lymphocytes and large mononuclear cells. A few arteries over the

convexities of convolutions showed endarteritis fibrosa. In the subjacent cortex of some areas there was diffuse atrophy of the superficial layers, with an increase of microglial cells and of blood vessels, mainly capillaries. The appearances as a whole, therefore, were indicative of healing, with slight residual chronic changes in the meninges and focal low-grade ischæmic alterations in the cortex.

Associated Lesions

Spreading Osteomyelitis of the Skull.—The commonest associated lesion (Table III) is spreading osteomyelitis of the skull, and most often this is secondary to chronic infection of the accessory nasal sinuses (nineteen cases). An acute exacerbation of the sinus infection, or some surgical procedure such as a nasal or external operation on the paranasal sinuses, or tooth extraction, has often appeared to precipitate the onset of pachymeningitis. Osteomyelitis was found more commonly at clinical examination and at operation than at necropsy. In some cases it appeared to be of rapid development, and was quickly followed by pachymeningitis ; in others it was a more chronic process lasting for weeks or even months. (Plate IVa).

In the acute form there was œdema and venous engorgement of the scalp ; at operation the pericranium stripped easily and the exposed bone oozed blood from many points. Sometimes there was an extradural abscess. In the diploe beads of pus were often seen. In the acute stage radiographs often showed no abnormality ; but later, in the cases which recovered, areas of osteomyelitis could be identified as irregular lines of diminished density enclosing areas of normal looking bone (Fig. 4), and sometimes a layer of new bone could be seen between the inner table of the skull and the dura. In patients treated with penicillin there was sometimes no abscess or sequestrum-formation from these areas, and the only evidence of spreading osteomyelitis was radiographic ; in other cases subpericranial abscesses formed and pus and a few spicules of bone discharged from various points in the skull. At necropsy, near the site of primary infection in the paranasal sinuses or mastoid, sequestra of various sizes were found ; and in one case, in which infection had spread from the maxillary antrum, there were chronic abscesses embedded in dense fibrous tissue in the pterygoid muscles and these were in contact with the inferior surface of the adjacent greater wing of the sphenoid.

When the osteomyelitis was mainly unilateral the subdural suppuration occasionally involved the contralateral cerebral compartment.

Extradural Abscess.—Extradural abscess, a sequel of osteomyelitis, may precede or accompany pachymeningitis and in the latter case may even be at a distance from the primary source of the infection (Case 2).

Thrombosis and Thrombophlebitis.—Thrombosis of the large dural sinuses, especially the superior longitudinal sinus, and retrograde purulent thrombophlebitis extending into the superficial cerebral veins was less common in our series than in that of Kubik and Adams (1943). When it occurs purulent leptomeningitis is superimposed upon the non-purulent subarachnoid inflammation which has already been described, at any rate in the region of the affected veins and sinuses. As a further sequel to venous thrombosis there are profound circulatory disturbances in the adjacent brain : severe degeneration of the neurones is accompanied by gross œdema, proceeding to venous infarction and hæmorrhages. Spread of infection by the perforating veins may result in suppuration in already softened areas. The patient usually succumbs before a well-defined cerebral abscess is formed ; but clinically, since the introduction of penicillin, we have encountered one or more large abscesses in the brain some weeks after the onset of pachymeningitis (Plate III).

Thrombosis may occur in one or more superficial cerebral veins without sinus-thrombosis and without infection of the leptomeninges. As a sequel, severe circulatory disturbances may occur in the subjacent cortex, with œdema and patchy neuronal degeneration which may go on to necrosis.

When purulent leptomeningitis complicates pachymeningitis, venous thrombosis is again a frequent sequel. Diffuse superficial encephalitis accompanies the more severe infections, with some polymorphonuclear infiltration in the early stages and, later, infiltration with mononuclear macrophages and proliferation of small blood vessels where destruction of cortical tissue has occurred.

Ventriculitis.—Ventriculitis was uncommon unless much surgical intervention, such as multiple needlings for abscess, had assisted the passage of infection.

Thrombosis of the Carotid Arteries.—Thrombosis of the carotid arteries in the neck was probably present in one of our cases (Case 4).

Lung Involvement.—Lung abscess and purulent bronchopneumonia were seen, and in this connexion it must be noted that Williams (1944) has described a group of cases of pansinusitis accompanied by bronchiectasis. Some of our cases of purulent pachymeningitis may have had suppurative lung lesions before they ever got subdural infection.

Septicæmia.—Septicæmia was observed in some of our cases at necropsy but we did not obtain any positive blood cultures during life, nor have we got unequivocal evidence of its presence in purulent pachymeningitis uncomplicated by osteomyelitis of the skull and other infective lesions known to produce septicæmia.

Purulent pachymeningitis is no exception to the rule that in intracranial infections almost any combination of infective lesions may arise. The valuable histological studies of Turner and Reynolds (1931) have demonstrated the diverse channels by which infection from the paranasal sinuses and mastoid process may spread into the cranium. In the past the infection has often spread so rapidly that it has been impossible to follow the trend of events clinically; and furthermore the risk of spreading the infection by opening the dura or puncturing of the lateral ventricles through an infected field has precluded investigations which might have materially assisted in diagnosis. But now the march of infection is often slowed with antibiotics, and the risk of spreading infection by surgical diagnostic measures such as ventricular puncture becomes greatly reduced. Cases that formerly would have been hopeless can now be cured by antibiotics and operative removal of purulent lesions. Consequently the habits of spreading intracranial infection assume a new importance.

In purulent pachymeningitis the starting point of infection is usually the skull: either the bone around the paranasal sinuses, or the petrous bone, or some other part of the skull infected by metastatic spread from a distant source. The sequence, usually, is osteomyelitis, extradural abscess, purulent pachymeningitis, also sometimes sinus thrombosis or thrombophlebitis of the cerebral veins; and terminally leptomeningitis. Extension to the brain itself is rarely of any magnitude in the cases not treated with antibiotics, for they are too soon fatal; but cerebral abscess may develop in the cases subjected to penicillin.

Less commonly there is simultaneous lepto- and pachymeningitis; or leptomeningitis may even precede pachymeningitis, as in one of our pneumococcal cases.

Thus, even without any consideration of spreading intracranial infection which does not involve the subdural space, there is an almost bewildering array of clinical possibilities, and the clinical picture is important in indicating the trend of events. This is one of the reasons why all those who are interested in intracranial infections should become familiar with the syndrome of purulent pachymeningitis.

The Clinical Picture

With early penicillin treatment the full clinical syndrome may not be seen. For recognition of the partial forms it is necessary to understand the complete form, and this will now be described. The clinical picture is distinctive (Cairns, 1930; Kubik and Adams, 1943). For a few hours the patient, who is usually in hospital for accessory nasal sinus or mastoid disease, may be restless and unlike himself, feverish, and perhaps complaining of headache. Then an arm or leg becomes weak, the eyes show persistent deviation away from the side of the paralysed limb and weakness of conjugate deviation to the opposite side, and within twenty-four hours the patient has a complete flaccid hemiplegia. The hemiplegia is frequently preceded by focal motor fits. [If the dominant hemisphere is involved difficulty of expression may be the first symptom and the patient soon becomes grossly aphasic.]

As the infection spreads in the subdural space it is often possible to demonstrate a complete homonymous hemianopia, and, if speech and consciousness are retained, severe sensory loss in the paralysed limbs (Case 1). More usually the patient is aphasic or drowsy and all that can be discerned is an absence of response to menace from the appropriate side and delayed appreciation of painful stimuli of the affected limbs. In short, the signs are those of a cortical paralysis of one cerebral hemisphere.

When the condition arises from mastoid infection or spreads from the maxilla to the middle cranial fossa the subdural pus may first spread over the base of the brain, and the prominent initial symptom then may be drowsiness. But even in these cases hemiplegia and homonymous hemianopia ensue with considerable frequency, even though the subdural pus is mainly on the inferior and medial surfaces of the hemisphere instead of mainly on the convexity, as it is when the infection arises from the frontal sinuses.

Intracranial pressure rises and papillœdema of mild or moderate degree may develop. There is often some stiffness of the neck, and the clinical observer may thus be surprised to find that the lumbar cerebrospinal fluid contains no more than 100 to 300 white cells per c.mm. and no organisms. In these circumstances it may be tempting to make a diagnosis of cerebral thrombophlebitis. The clinical pictures of the two conditions may resemble one another closely, and differential diagnosis is complicated by the fact that purulent pachymeningitis is often, though by no means invariably, accompanied by thrombosis of the cerebral venous sinuses and veins. But there are certain distinguishing features.

Firstly, there is the history of chronic pansinusitis ; in our experience uncomplicated cerebral thrombophlebitis is uncommon in such cases. Secondly, there are the signs of osteomyelitis preceding or accompanying the neurological illness—œdema and venous engorgement of the scalp, temple, or face over the affected bones—high fever (102° to 105° F.), and sometimes rigors ; with osteomyelitis of the facial bones there may be also trismus and severe facial pain.

Purulent Pachymeningitis before the Discovery of Penicillin

Case 1. *Pansinusitis. Bilateral antrostomy and drainage of frontal sinuses. Spreading osteomyelitis of face and skull. Purulent pachymeningitis* (*Strep. viridans*). *Death.* (No. 2788, 1936, a patient of Mr. F. C. Capps.)

A male, aged 47, with chronic pansinusitis, developed an infected mucocele of the frontal sinus with a lump on the forehead. Pressure on the lump produced a discharge of pus from the right nostril. Three months later both antra were drained of foul pus by the nasal route (hæmolytic streptococcus and in small numbers *Staphylococcus aureus*), and drainage of the frontal sinuses was established by removal of the anterior ends of the middle turbinate bones and external resection of the inner part of the floor of the right frontal sinus. For nine days the patient did well, and then he developed a spreading osteomyelitis of the facial bones with fever, swelling, and abscess formation about the eyes and upper jaw, for which further operations were required. His wounds discharged much pus and he became weak, wasted, and anæmic.

He was given sensitized streptococcal vaccine, prontosil, and blood transfusions, but the facial osteomyelitis continued and, twelve weeks after its onset, spread to the frontal bone. During the next five weeks the osteomyelitis gradually extended backwards (Plate IV a) and the patient had headaches, facial pain, and slight fever, and became much more irritable.

Purulent pachymeningitis first showed itself on Feb. 4, 1937, about sixteen weeks after the onset of facial osteomyelitis. The patient noticed a weakness and numbness of the right leg, and twelve hours later slight numbness and difficulty of control of the right hand ; he vomited twice, and had slight headache and fever (100·4° F.). On examination there was moderate weakness and hypotonia of the right limbs, the leg being worse than the arm. The tendon jerks of the right limbs were increased, the right abdominal reflexes were absent ; both plantar reflexes were flexor. In the right big toe passive movements were not appreciated, and in the right thumb the threshold of appreciation of the direction of passive movements was raised. Cotton wool was felt normally on the right upper limb and trunk, but on the right lower limb was felt only on strong stimulus and as a cold, tickling sensation. Pin point was felt on the right foot as a cold sensation, on the right leg and thigh as a spreading tingling sensation, on the trunk and upper arm normally as a pin, on the right forearm as a tingling sensation, and on the right hand as a blunt pin.

About eighteen hours after the onset of sensori-motor signs the patient began to show slight dysphasia and an attention defect in the right homonymous fields. On the next day, Feb. 5, he had gross defect of understanding and of expression. His right lower limb was completely and his right upper limb almost completely paralysed, his left leg at times was clumsy and weak, and light stroking of each foot produced an unpleasant over-reaction. He was incontinent of urine and fæces, and his neck was slightly stiff.

Operation in the left parietal region (Feb. 5) showed gross osteomyelitis with subpericranial pus and granulations on the outer surface of the dura. When the dura was opened thick pus was found free in the subdural space, and small amounts could be collected for some time by depressing the brain away from the dura. The left parietal lobe was needled, but no abscess was found. Films of the pus showed pus cells and streptococci, and cultures yielded *Streptococcus viridans*.

The patient grew steadily worse and died on Feb. 9.

As there was no necropsy we cannot exclude the possibility that there was also a thrombosis of the sagittal sinus and cerebral veins ; our necropsy studies on other cases suggest that such lesions usually do not alter the clinical picture in the acute stage.

Because of the relatively late development of aphasia this case shows particularly well the progressive loss of cortical function—flaccid hemiplegia becoming complete in two days and spreading to involve the opposite leg, widespread and rapid sensory loss with paræsthesiæ and over-reaction, aphasia, and homonymous hemianopia. The patient died five days after the onset of neurological symptoms.

In earlier days spreading osteomyelitis of the skull of this type was treated by widespread removal of bone, but with little success. Of twenty cases of diffuse osteomyelitis following operations on the paranasal sinuses all died (McKenzie, 1913). In Case 1 this treatment could not be employed early because the facial bones were so widely affected. Prontosil and vaccines did not materially arrest the spread of the disease.

Purulent pachymeningitis does not always run such a rapid course. Plate II a shows the brain of a man of 42, in whom the illness lasted for thirteen days, during which flaccid left hemiplegia and aphasia (he was a left-handed man) fluctuated in intensity. On some days there would be improvement in tone and return of power in the paralysed limbs, with improvement in understanding and occasionally, but only to a slight degree, of speech. Thus, one day the left upper limb was flaccid and completely paralysed ; next day tone was normal, good power was present at all joints, and the ergometer record of the left hand-grip was

30 as compared with 45 on the right. On some days, when the left upper limb seemed quite flaccid and paralysed, with strong exhortation the patient would suddenly flex it voluntarily at the elbow, through a considerable range. This phenomenon suggests that the paralysis differs from that caused by compression of the pyramidal tract or precentral gyrus by tumour, and that it results from a lesion at a higher level than the precentral gyrus. It is indeed remarkable that a relatively thin film of pus in the subdural space can produce such complete hemiplegia. Blood accumulating in the subdural space at the same rate does not produce the same degree of paralysis, if indeed it produces any. Nor does subarachnoid pus have the same effect; indeed it is uncommon to see complete motor paralysis of a limb in purulent leptomeningitis. Subdural pus spreads more rapidly than subarachnoid pus, and it may be that it is the diffuseness of the cortical involvement which is the essential cause of the cortical paralysis.

Terminal Events.—Without penicillin the majority of our fatal cases (eighteen out of twenty-six) have died within two weeks of the onset of neurological symptoms. Signs of spread of the subdural suppuration to the opposite hemisphere appear in the form of paralysis, with or without motor fits, of the hitherto healthy side. Severe rise of intracranial pressure evidently contributes to death in a considerable proportion of cases, for at necropsy there is often severe herniation of the uncinate gyri through the tentorial opening and of the cerebellar tonsils through the foramen magnum. We have even seen hæmorrhage into one herniated cerebellar tonsil, which is an indication of rapid and severe herniation. Pulmonary complications and in one case renal failure have contributed to death.

Modification of the Clinical Picture in Cases Treated with Penicillin.—With adequate systemic penicillin in the early stages of the illness the clinical picture may be modified. There may be no obvious signs of osteomyelitis of the vault of the skull, hemianopia may be absent or incomplete, and the overt motor and sensory paralysis may be limited to one limb. The condition can still be recognized by the fact that signs of cortical paralysis come on suddenly after gross infection of the paranasal sinuses or petrous bone and without obvious leptomeningitis, but differential diagnosis from cerebral thrombophlebitis may be very difficult without exploration of the subdural space by means of burr-holes. Diagnosis is made more difficult by the fact that with penicillin and inadequate surgery in the early stages purulent pachymeningitis may be complicated by cerebral abscess.

TABLE IV

DISTRIBUTION OF TYPES OF STREPTOCOCCI

	Total Strep. cases	Detailed records	Anærobic	Viridans	β-hæmolysis
Sinus infection	18	13	8	4	1*
Mastoid infection	3	1	1	0	—
Distant causes	3	3	1	2	—
Total	24	17	10	6	1*

* In addition 1 patient with anærobic streptococcal infection showed also at subsequent drainage of a subdural loculus β-hæmolytic streptococcus (Case 3).

Bacteriology

The predominant causal organisms in our series were streptococci of anærobic, or viridans, or non-hæmolytic forms (Tables I and IV). Staphylococcus and β-hæmolytic streptococcus were rare, although the pus from the paranasal sinuses of our cases usually contained a combination of these two organisms. This is a remarkable finding when we consider that osteomyelitis of the skull is as often caused by *Staphylococcus aureus* as by non-β-hæmolytic streptococci. Comparing our cases of osteomyelitis of the skull with and without purulent pachymeningitis (Table V) it is seen that when there is no subdural infection staphylococcus is the preponderant organism, whereas when there is subdural infection streptococcus, almost invariably non-β-hæmolytic, is significantly preponderant. The staphylococcal infections tend to become localized, and though they may produce brain abscess they do not cause purulent pachymeningitis; the streptococcal infections tend to spread along the skull and also through the dura.

The streptococci found in our series were usually

TABLE V

BACTERIOLOGICAL COMPARISON OF OSTEOMYELITIS OF THE SKULL WITH AND WITHOUT PURULENT PACHYMENINGITIS

22 unselected cases of osteitis of skull:	Strep.	Staph.	Strep. and Staph.	Other	No record
With purulent pachymeningitis	19	1	1	—	1
Without purulent pachymeningitis	5	14	1	—	2

in short chains though occasionally in very long chains and sometimes pleomorphic. They often proved difficult to grow and were usually anærobic or microærophilic. Sometimes they showed unusual pigmentation reactions. Now that these patients are apt to be treated with systemic penicillin for a few days before the specimen of subdural pus is obtained by operation the difficulties of cultivation may be greater, requiring the routine use of penicillinase with cultures.

Similar types of streptococci have been observed in spreading osteomyelitis of the skull by Williams and Heilman (1937) and Williams (1944). The same groups of streptococci are also probably today the most common cause of brain abscess uncomplicated by spreading osteomyelitis of the skull or purulent pachymeningitis; also organisms of the viridans group produce meningitis after cranial operations. And it is interesting to recall that in the final stages of the 1939–45 war, when penicillin was freely available, the non-β-hæmolytic streptococci were the most serious menace in brain wounds (Cairns and others, 1947). Their identification and classification are as yet far from complete (see Sandusky and others, 1942, and Sherman, 1937, for recent reviews), but evidently are of increasing importance in human disease now that, as a result of penicillin, infections with *Staphylococcus aureus* and β-hæmolytic streptococcus are diminishing in frequency and severity.

We had one case of purulent pachymeningitis due to pneumococcus, type VII, and in this case the route of infection appeared to be different; after acute frontal sinusitis and extradural abscess the patient developed purulent leptomeningitis and within about two days signs of purulent pachymeningitis. There was no evidence of spreading osteomyelitis of the skull (Cairns and Russell, 1946, Case 5).

Penicillin Sensitivity of Non-β-hæmolytic Streptococci.—The cases which we have been able to treat adequately with penicillin have shown good clinical response to treatment. The sensitivity of the organisms to penicillin *in vitro* was recorded in only four cases. In two, one an anærobic streptococcus, the other an α-hæmolytic organism of the viridans group (Case 2) the organism was completely inhibited by 0·04 units per c.cm. of penicillin, while in a third a non-hæmolytic streptococcus was completely inhibited by 0·01 units per c.cm. In the fourth Dr. E. S. Duthie found that the organism, a short-chained streptococcus which grew without hæmolysis under ærobic and anærobic conditions, was completely insensitive on blood plates to penicillin at the usual dilutions. There was some inhibition by 20 units per c.cm. but none by 5 units per c.cm. This organism was also insensitive to sulphathiazole, sulphapyridine, and sulphadiazine. The patient showed no response to limited chemotherapy, which, owing to shortage of supplies, did not include systemic penicillin.

Theory of Treatment

With very few exceptions the organisms producing purulent pachymeningitis are sensitive to penicillin, even the anærobic streptococci (Hempstead, 1944), though some of these may be relatively resistant and require much larger doses than are adequate against *Staph. aureus* and β-hæmolytic streptococcus. In most cases of purulent pachymeningitis infecting organisms are present not only in the subdural space, but also in the skull and facial bones, and probably on occasions in the leptomeninges. In some cases there may also be macroscopic collections of pus in the extradural space and in the brain substance as well as in the subdural space, and there may be infected clot in the sagittal sinus and cerebral veins. To combat these areas of infection it is necessary to give penicillin by three routes, and macroscopic collections of pus must be removed by operation since they usually cannot be sterilized by penicillin.

Penicillin

Subdural Injection.—Systemic penicillin passes freely into the subdural space (Table II) and it is possible that an adequate amount might be supplied there by very large and frequent intramuscular doses. Our limited experience suggests, however, that it would be unwise to rely exclusively on the systemic route (Case 6). Subdural injections can produce a higher concentration in the subdural space, and moreover the mechanical effect of the injected solution must aid in providing access of the drug to the organisms and also in preventing loculation of the pus. Furthermore, since penicillin passes rapidly from the subdural space into the blood stream (Smith, Duthie, and Cairns, 1946, Case 8) by way of the dural veins, which have free communication with the diploic veins of the overlying skull, it is probable that high values of penicillin are obtained in the infected coverings of the subdural space. Elder (quoted by Robertson, 1900) found that coloured injections into the subdural space of a recently killed animal very quickly passed through the dura into the veins both of this membrane and of the skull.

The penicillin is instilled directly into the space, through an in-dwelling catheter, at intervals of three to four hours, since it is rapidly absorbed by the blood stream.

Systemic Injections.—Systemic penicillin passes

into fluids in the subdural space (Smith and others, 1946; Cairns, 1947). It is also required to combat the infecting organisms in the skull or elsewhere. As these organisms may be relatively resistant to penicillin, large doses should always be employed systemically—not less than 100,000 units every three hours until the sensitivity of the organism *in vitro* has been tested. Experience shows that the skull infections may persist for a long time, even under treatment, and relapse may follow promptly if penicillin is withdrawn too soon (Case 2). Therefore systemic injections should be continued for at least eight weeks.

Subarachnoid or Ventricular Injection.—Subarachnoid injections are of no use for the pachymeningitis, but may be required for the associated leptomeningitis. It is now definitely established that only traces of penicillin pass from the blood to the cerebrospinal fluid and that patients with meningitis, for example pneumococcal meningitis, can relapse while undergoing full systemic treatment only; also that penicillin injected into the subdural space does not reach the subarachnoid space (Case 2; also Smith and others, 1946, Case 8). Although in the early stages leptomeningitis is usually slight, it is probably wise to give lumbar or ventricular injections of penicillin (10,000 to 15,000 units per c.cm.) once daily in the first days of treatment, or longer if the cerebrospinal fluid contains organisms or many pus cells. Sulphadiazine by mouth, with due precautions against renal block, is also very useful for a continuing mild leptomeningitis.

The surgical procedures necessary in the treatment of purulent pachymeningitis frequently entail risk of contamination of the cerebrospinal pathways: for example when a brain needle seeking for a subdural loculus enters the lateral ventricle. In such circumstances a prophylactic dose of penicillin should be injected into the ventricle.

Operative Treatment.—In purulent pachymeningitis exploration of the subdural space does not usually yield a large amount of pus, and the surface of the brain quickly plugs the drainage hole in the dura. The most satisfactory method is instillation of penicillin solution through one or more catheters (Plate IV b); this tends to wash out the pus, to spread penicillin to all parts of the subdural space, and, if done sufficiently early and often, to prevent the development of loculated subdural abscess.

Wide surgical removal of the infected skull and facial bones in the acute stage can no longer be considered necessary, for under penicillin treatment most of the osteomyelitis will subside without obvious sequestration. But usually there will be one or more areas in which osteomyelitis goes on to necrosis, sequestration, local subaponeurotic abscess, and sinus formation. Though even this may subside satisfactorily under continued systemic penicillin, assisted by the spontaneous discharge of pus and bone spicules (Case 2), it is wiser to remove the residual necrotic or suppurative foci of osteomyelitis in the subacute or chronic stage in order to diminish the risk of subsequent relapse of cranial or intracranial infection. In facial osteomyelitis it may be impossible to remove all the infected bone; in such cases it would probably be necessary—we have not had personal experience on this point—to continue systemic penicillin uninterruptedly for months.

It has now been fully established that penicillin cannot gain access to any large collection of pus in sufficient amounts to sterilize it, and therefore an essential part of the treatment is evacuation of such collections. The surgeon must therefore be ever on the alert to detect localized collections of pus in the subdural space or elsewhere, and on the apparently healthy side as well as on the side which is obviously involved. The associated pyogenic lesions include extradural abscess, brain abscess, and suppurative thrombosis of sagittal or lateral sinuses. Loculated subdural abscess is the most common sequel of the spreading purulent pachymeningitis, especially on the medial and inferior surfaces of the cerebral hemisphere.

Experience since the Introduction of Penicillin

All our patients treated before the discovery of penicillin died (Table VI). Also all patients died who, owing to shortage of supplies in the early days of penicillin, could not be given the drug systemically and were treated only by the subdural route; however in some of these the clinical picture was modified. Largely as a result of attenuation of the infection by penicillin we recognize three clinicopathological groups of cases according to the behaviour of the intracranial suppuration under treatment: (1) uncomplicated purulent pachymeningitis (5 cases); (2) purulent pachymeningitis

TABLE VI

RESULTS OF TREATMENT

Dose of penicillin	Died	Recovered	Total	Loculated subdural abscess
None ..	18	None	18	7
Inadequate	5	None	5 } 15	3 } 9*
Adequate ..	3	7	10 }	6 }
Total ..	26	7	33	16

* Combined in 3 cases with cerebral abscess.

TABLE VII

CLASSIFICATION OF CASES TREATED WITH PENICILLIN

Clinico-pathological group	Penicillin			
	Adequate		Inadequate	
	No. of cases	Died	No. of cases	Died
Uncomplicated purulent pachymeningitis	3	—	2	2
Pachymeningitis followed by loculated subdural abscess	5	2	1	1
Pachymeningitis plus subdural abscess plus cerebral abscess	2	1	2	2
Totals	10	3	5	5

followed by loculated subdural abscess (6 cases); (3) purulent pachymeningitis followed by loculated subdural abscess which in turn is followed by cerebral abscess (4 cases) (Table VII).

Uncomplicated Cases.—The following is an uncomplicated case which illustrates the therapeutic methods and the stages of recovery; and it was probably the first case of purulent pachymeningitis to be treated successfully with penicillin, which Sir Howard Florey kindly provided from his meagre stocks early in 1943.

Case 2. Pansinusitis. Bronchopneumonia and empyema. Acute osteomyelitis of skull and purulent pachymeningitis (Strep. viridans). Evacuation of subdural pus. Penicillin by subdural and systemic routes. Recovery. (No. 5912.)

A private, aged 28, on enlistment in the Army in 1940 was found to have severe dental sepsis, but he had never been ill until April 9, 1943, when he developed pain and swelling of the left eye, with fever up to 103° F. These symptoms continued, and were accompanied by cough and pain in the left side of the back and neck. On April 16 he was admitted to a military hospital with a temperature of 102·6° F., a pulse rate of 100, and respirations 20 per minute; he had a purulent blood-stained discharge from the left nostril, and was acutely tender over the occipital muscles on the left side. Radiographs showed opacity of both maxillary antra and of the left ethmoid sinus, and slight haziness of both frontal sinuses. On April 18 he developed bronchopneumonia at both bases, with a pleural rub on the left side. He was given full doses of sulphathiazole for five days without improvement.

On April 22 both maxillary antra were punctured and irrigated. The bone was unusually soft. Thick, green pus was obtained from each side, and from the left side a large slough. On the following morning he was worse: previously co-operative and courteous, he was now surly and taciturn; in the afternoon he became confused and restless, and did not recognize his wife. On the morning of April 24 he developed aphasia and right brachial monoplegia, and during the day he became increasingly drowsy. He was transferred to the Military Hospital for Head Injuries, Oxford.

On admission his temperature was 102·4° F., the pulse rate 108, and respirations 40 per minute. He was slightly cyanosed and drowsy, but easily roused. He understood only simple commands, and was completely mute, with slight dysphagia, moderate neck rigidity, gross engorgement of arteries and veins of the scalp, with slight generalized œdema and engorgement of retinal veins. There was no response to menace in the right homonymous visual fields, and slight bilateral proptosis, more marked on the left side. There was slight weakness of the right side of the face, complete flaccid paralysis of the right upper limb, moderate weakness of the right lower limb, absence of right triceps and supinator jerks, and diminution of right biceps and knee jerks; but the right ankle jerk was normal. Abdominal reflexes were absent on the right side and greatly diminished on left; the plantar reflexes were normal. He had delayed appreciation of pin-prick on the right side. Signs of consolidation at the bases of both lungs were more marked on the left side. Lumbar puncture showed an initial pressure of 300 mm.+, a total protein of 80 mg. per 100 c.cm., white cells 44 per c.mm. (mainly polymorphs); cultures were sterile. Blood culture was sterile, and blood sedimentation rate 53 mm. in the first hour. There was slight secondary anæmia (white blood cells 14,200 per c.mm.).

Operation: April 24.—Through a right parietal burr-hole the bone looked normal. There was a small amount of clear fluid in the subdural space, and the arachnoid looked normal and was flush against the dura. Through a left frontal burr-hole thin pus escaped from the diploe. The left subdural space contained thick pus which escaped whenever the brain was displaced away from the dura; 5 c.cm. were collected. A rubber catheter was passed through the burr-hole to the posterior end of the subdural space (Plate IVb) and 5 c.cm. of calcium penicillin solution (1,250 units) were injected through it. The scalp was unusually vascular, and much more blood was lost than is usual in such a small operation. Blood transfusion (1 pint) was given.

Bacteriology.—Films of the diploic and subdural pus showed Gram-positive cocci in clumps and chains. On culture this organism proved to be α-hæmolytic and was provisionally classified as *Streptococcus viridans*. It was completely inhibited by penicillin 0·04 units per c.cm., but gave normal growth in serum broth containing 10 mg. of sulphapyridine per cent. (Drs. B. Moore and Margaret Jennings).

Penicillin Treatment.—By the intramuscular route 120,000 units were given daily between April 24 and May 11 (1,820,000 units), and 90,000 units daily between May 16 and May 24 (706,000 units). Into the left

subdural space between April 24 and May 20 153,000 units were administered (5 c.cm. of a 250 units per c.cm. solution, three-hourly until May 7 and thereafter less frequently). Intrathecally (at the conclusion of the lumbar punctures between April 24 and May 9) 10,000 units were given.

In addition blood transfusions were given on several occasions, and for the first four days after operation an intravenous saline drip. For the first two weeks, owing to dysphagia, feeding was by nasal tube.

Progress.—On April 26 (two days after initiation of treatment) the general condition was improving. The patient was more alert and fairly strong, and voluntary power suddenly returned to the proximal joints of the right upper limb. The right plantar reflex was now extensor. There was delayed appreciation of pin prick on the right side, as before. There was less engorgement of the scalp vessels, but the scalp was still œdematous. There was slight bilateral papillœdema with one retinal hæmorrhage. In the afternoon he had a generalized convulsion, involving the right limbs more than the left, followed by a state of spasticity with increased tendon jerks of the right limbs.

By April 29 there had been no further improvement in the power of the right limbs. He was still speechless and more drowsy. Dullness at the base of the left lung had increased. The left chest was explored by needle, and 5 c.cm. of thin pus, containing in films and cultures a streptococcus identical with that obtained from the subdural space, was aspirated.

On April 30 he was drowsy and at times restless. Pus discharging from the left frontal burr-hole showed poorly-stained streptococci. Owing to the lack of improvement it was feared that pus might be pocketing in the posterior part of the subdural space. A left parietal burr-hole was accordingly made. The surface of the brain looked healthy ; when it was pressed away from the dura 10 c.cm. of subdural pus were obtained, similar in character to that from the left frontal region and yielding a very slight growth of streptococcus. A right frontal burr-hole was also made and from the diploe came pus which showed in films Gram-positive cocci, mostly intracellular, and sterile in culture. There was a thin layer of new bone on the inner table of the right frontal region. When the dura was opened about 1 c.cm. of thin fluid was obtained, and the brain looked healthy.

On May 2 there was increase of papillœdema, still some engorgement of the scalp vessels and gross œdema over the posterior part of the vertex. Radiographs showed a circular area (4 by 4 cm.) of osteomyelitis in the mid-frontal region (Plate V a), scattered areas of rarefaction alongside the posterior part of the sagittal suture, changes in the bony outlines of the frontal sinuses, and gross opacity of both maxillary antra and of the left ethmoidal sinuses.

On May 7 speech returned, monosyllabic and slurred. Comprehension was still impaired. The scalp was no longer engorged, and œdema was less. By May 9 sensation of the limbs was normal. Chest signs had disappeared. Radiographs showed no spread of the osteomyelitis of the frontal bone. Nasal feeding was stopped as he could now swallow well. By May 11 power was improving and he was sitting up in bed, though he still had partial right homonymous hemianopia. He was no longer incontinent of urine. Systemic penicillin was stopped, owing to shortage of supplies.

On May 16 he complained of frontal headache and said he was not so well. There was considerable discharge of pus from the right frontal burr-hole (intracellular cocci, but cultures sterile). The scalp was again engorged. Osteomyelitis had evidently recurred, but without worsening of neurological signs. Systemic penicillin was resumed.

By May 20 speech and understanding, and also power of his right limbs had improved. The left subdural tube was removed and subdural penicillin stopped. On May 24 systemic penicillin was stopped again and a course of sulphanilamide begun. He was gaining weight rapidly. On June 1 extracranial pus aspirated from the region of the right frontal burr-hole contained the infecting organism. Dr. Jennings found that there had been no reduction of its sensitiveness to penicillin.

Subsequent course.—From this time onwards his general condition steadily improved ; he was up and about and from July was performing light tasks in the hospital. From time to time pus discharged from the right frontal incision, but this stopped early in July after a course of local penicillin injections through the skin sinus. About this time he had pain in the right side of the chest ; in August he developed a cough and had slight hæmoptysis, and radiographs showed an area of opacity in the middle lobe of the right lung, suggesting consolidation (Plate V c) ; this had practically disappeared without any signs of cavitation by November, 1943 (Plate V d) at which time he was discharged from the Army.

Soon after leaving hospital early in 1944 he took up work, and he remained in regular employment—though with several changes of job—up to the time when he was last seen in May, 1947. He was a person of little education and poor intelligence, and tests by Major W. R. Reynell during his convalescence had shown a gross defect of abstract thinking and inability to learn new activities. Between January, 1944, and May, 1947, he had eleven sensori-motor epileptic attacks of the right upper limb, in one of which he lost consciousness. On neurological examination in 1947 the only remaining sign was very slight weakness of the right upper limb, sufficient to interfere with his holding money or a cigarette in his right hand but not otherwise disabling. His accessory nasal sinuses and lungs had given no trouble.

In this case, owing to shortage of supplies, the amount of penicillin given systemically was necessarily much less than the optimum dose. In the subdural space large quantities of dilute penicillin solution, a total of 612 c.cm. (250 units per c.cm.), were instilled through an in-dwelling catheter at frequent intervals for twenty-seven days. This

produced no symptoms, unless we are to regard the solitary focal fit on the second day of treatment as due to the penicillin. A little of the solution escaped around or through the catheter immediately after the injections, but very little drained away at other times. The small amounts of penicillin injected into the subarachnoid space, 1,250 units at the conclusion of each lumbar puncture, as a prophylactic measure were probably unnecessary, for there were never more than 43 white cells per c.mm. in the cerebrospinal fluid ; though on one occasion (May 1) a few degenerate cocci were seen in films of the cerebrospinal fluid.

The causal organism, an atypical *Streptococcus viridans* which was very sensitive to penicillin, disappeared from the subdural fluid some time in the second week of penicillin treatment, but was still present in the pus from the bone eight weeks after penicillin treatment was begun, when it was still as sensitive to penicillin as at the beginning of treatment. Withdrawal of systemic penicillin after eighteen days was promptly followed by recrudescence of osteomyelitis of the skull, with headache and discharge of pus from the right frontal region. In the light of subsequent experience it is remarkable that the diffuse osteomyelitis of the skull was controlled with such small amounts of systemic penicillin given through such a relatively short time (twenty-seven days in all). And it is still more remarkable that the osteomyelitis, which is known to have extended back to the parietal region, healed without any operative removal of necrotic bone (Plate V b). A few spicules of necrosed bone discharged from the right frontal burr-hole ; otherwise there was no obvious sequestration.

It was shown in this case and in another (Smith and others, 1946, Case 8) that penicillin in the subdural space does not escape into the cerebrospinal fluid. It is absorbed by the blood stream of the dura mater, which is connected with the overlying skull by very numerous fine vessels, and it is thus possible that during the twenty-seven days of subdural instillations the concentration of penicillin in the skull was considerably higher than would have been obtained with the small doses employed systemically. The fluid injected into the subdural space was freely absorbed : only a small fraction of the 612 c.cm. of penicillin solution injected during twenty-seven days escaped from the in-dwelling catheter.

As in Case 1, the symptoms produced by the subdural suppuration were those of a complete cortical paralysis of the left cerebral hemisphere, and the manner in which cortical function recovered is of considerable interest. Recovery from aphasia was slow. Though his understanding was improving, the patient remained mute for two weeks after treatment was begun and dysphasic for a further three weeks. The recovery of speech function was gradual and within a space of fifteen days the following stages were observed : first, monosyllabic answers to questions ; then a telegraphic type of utterance and simple sentences with considerable dysarthria ; then longer sentences which tailed off unintelligibly at the end ; then requests by name for certain objects ; then ability to give a moderately good account of what he read in the newspaper. There was nothing in this recovery of speech which in any way distinguished it from recovery after removal of a benign type of expanding lesion near the speech area.

The recovery of voluntary power, on the other hand, was unlike that of recovery after most cortical lesions. On the first day after penicillin treatment was begun the patient was unable to move his right upper limb though he tried hard to do so, and, failing, moved it passively with his left hand. Next day, 38 hours after the beginning of treatment, he could move the right upper limb strongly ; he maintained it outstretched in mid-air and could voluntarily hyperextend the wrist, though he was still unable to grip. Such remarkably rapid recovery is rarely seen in cortical lesions. The first sign as a rule is feeble movement at the proximal joints, and then there is a gradual increase of power with gradual return of function of the more distal joints. No further recovery was noted for a further two weeks, when at the same time as he started talking he became able to move his right fingers ; during the next week movements of the right hand became almost normal, though still for a few days slightly weak, and this weakness became noticeable again for a day six weeks after the onset of treatment. Subsequently, apart from slight clumsiness, his right hand was normal. There was never any increase of tone in his limbs.

Coincidently with the cranial and subdural infection there was a bilateral bronchopneumonia with, on the left side, a small empyema infected with the same organism. The empyema subsided with no more than a single aspiration of 5 c.cm. of pus, and the left lung also cleared up during treatment with systemic penicillin. Infection of the right lung subsequently recrudesced, but after six months and without chemotherapy the radiological signs of consolidation entirely disappeared.

This case and one other early in the penicillin series were the only ones in this series in which pachymeningitis was not complicated by some other intracranial suppuration. Subsequent cases have been complicated by loculated subdural abscess, followed or not by cerebral abscess.

Purulent Pachymeningitis followed by Loculated Subdural Abscess.—Plate II b shows a loculated subdural abscess. This was in a man who developed intense pneumococcal leptomeningitis after frontal sinusitis and extradural abscess. He was treated by lumbar and systemic penicillin, and when on the tenth day of his meningitis we made parietal burr-holes in order to inject penicillin into the ventricles we unexpectedly found free pus in the subdural space on the left side. This was successfully treated by subdural instillations of penicillin through an in-dwelling catheter, and the patient seemed to be progressing favourably until, on the thirty-fifth day of meningeal infection, he developed signs of a right-sided cerebral abscess ; 100 c.cm. of pus was aspirated through a brain needle, and the pyograms —after injection of thorotrast—showed that the pus was not intracerebral but was in the subdural space on the right of the falx. No pus had been seen over the convexity of the right cerebral hemisphere at any of the subdural explorations. This patient died seven weeks after the onset of meningitis. Detailed findings have been reported elsewhere (Cairns and Russell, 1946, Case 5). The post-mortem specimen (Plate II b) shows a collapsed chronic abscess cavity with thick walls, in places crenated in outline, lined on the one side by falx and tentorium, on the other by the medial and inferior surfaces of the right cerebral hemisphere. This is the lesion which has given us so much trouble in our later cases, of which the following is an example.

Case 3. *Pansinusitis. Frontal osteomyelitis. Purulent pachymeningitis and leptomeningitis* (*anærobic streptococci*). *Loculated subdural abscess. Penicillin and multiple drainage operations. Recovery.* (R.I. 29963, 1944.)

A rather frail boy, aged 11 years, suffered from chronic tonsillitis and adenoids, occasional asthma, and frequent winter colds. In April, 1944, three months before he came under our care, he complained of toothache and a swelling in his right cheek, and there was discharge of pus from the nose. He lost some schooling but was not severely ill until July 3, when he felt tired and took to his bed. On July 6 his right eye became bloodshot, and on the following day a painful swelling appeared on the right side of his forehead. He was admitted to hospital and on July 11 his right maxillary antrum was punctured and washed out. Next day he was found unconscious (probably following an epileptic fit). His neck was stiff and his right limbs did not respond to painful stimuli. On the same night he was transferred to the Radcliffe Infirmary.

On admission on July 12 he was thin, pale, dehydrated, and stuporose, and was unable to produce any articulate sounds. The temperature was 103° F., the pulse rate 110, and respiration rate 22 per minute. A fluctuant swelling, about 3 cm. in diameter, projected on the forehead above the right orbit. He had marked neck rigidity. His ocular fundi and pupils were normal. His right limbs were flaccid and paralysed and there was paralysis of conjugate movements of his eyes to the right and slight right lower facial weakness. His left arm was maintained in kataleptic attitudes. The tendon jerks were absent on the right, but present on the left ; his right plantar reflex was extensor and the left flexor in type. Sensory functions and visual fields did not seem to be impaired.

Radiographs showed opacity of the right maxillary antrum and thickening of the walls of the left antrum, impaired translucency of the frontal sinuses, and some destruction of the upper wall of the right frontal sinus. At this time no osteomyelitis was visible radiologically in the cranial vault. Lumbar puncture produced purulent fluid with an initial pressure of 370 mm., cells 7,900 (98 per cent. polymorphs per c.mm.), and protein 250 to 300 mg. per 100 c.cm. Films showed pus cells and a few streptococci ; cultures were sterile. The white blood cell count was 16,000 per c.cm.

During the following day he had three right-sided focal motor attacks affecting head, eyes, face, right shoulder, and upper limb, in that order, with incontinence of fæces. We made a diagnosis of maxillary sinusitis, leading to frontal osteitis, with Pott's puffy tumour, leptomeningitis, and left frontal subdural or possibly intracerebral abscess.

Immediate Treatment.—Penicillin was given by intramuscular drip (120,000 units in twenty-four hours), and into the lumbar theca (8,000 units twice daily) (Fig. 1).

At operation the lateral ventricles were tapped through bi-parietal burr-holes ; the cerebrospinal fluid under an initial pressure of 370 mm. was faintly cloudy, and penicillin 8,000 units, was injected into the right ventricle. No subdural pus was found in the parietal areas. Next, bi-frontal, coronal burr-holes were made. On the right side normal tissues were found ; on the left 6 to 8 c.cm. of greenish-white thick fœtid pus were found in the subdural space, and a purulent membrane obscured the view of the underlying cortex. A rubber catheter was tied in the subdural space, through which penicillin (10,000 units in 5 c.cm. of saline) was instilled, first at three-hourly, then at six-hourly intervals.

On the following day further burr-holes were made to determine the limits of the pus. A mid-frontal burr-hole, slightly to the left of the sagittal sinus just above the orbital roof, revealed subdural pus and another catheter was inserted into the left subdural space for drainage and penicillin instillations. A left anterior parietal and a left subtemporal burr-hole revealed normal conditions, thus showing that, as far as the convex surface of the brain was concerned, the subdural pus was confined to the left frontal area.

A pint of blood was transfused, and he was given phenobarbitone gr. ½ three times a day. He was fed by nasal tube. Four days after admission the Pott's puffy tumour in the right supraorbital region was aspirated ; 0·5 c.cm. of pus was removed and replaced by penicillin solution (2,500 units).

On the day after admission thick pus was obtained at lumbar puncture (250,000 cells per c.mm. ; streptococci in films, cultures sterile). This was quite unlike the

findings at lumbar puncture on previous and subsequent days, when the cerebrospinal fluid contained 7,500 white cells or less per c.mm. There was no evidence of blockage of the cerebrospinal pathways, and it is probable that this pus came from the spinal subdural space. We have seen pus in the spinal subdural space in a case of purulent pachymeningitis following gunshot wound of the brain.

Bacteriology.—The first specimens of lumbar and ventricular cerebrospinal fluid and the pus from the Pott's puffy tumour, showed streptococci but cultures were sterile. The subdural pus showed streptococci on films and streptococci were grown in anærobic cultures. Five days after treatment was begun the organisms had disappeared from the films taken from the cerebrospinal fluid (Fig. 1), and on the seventh day the subdural discharge had ceased. Sulphadiazine was added to the treatment on the eighth day.

Progress.—The focal fits continued in his right lower limb for five days; they were of short duration and inconspicuous. During the first fortnight he gradually became more alert and his right hemiplegia improved slightly. He began to talk in dysarthric monosyllables on the fifth day and later showed perserveration and nominal dysphasia. His neck rigidity became less marked. His temperature became normal during the third week, at which time he was still partly hemiplegic, occasionally incontinent of urine, and still not talking freely.

In the fourth week he began to deteriorate again, nine days after systemic penicillin had been stopped. His intracranial pressure rose (600 mm. plus by lumbar puncture), his temperature rose slightly, his leptomeningitis increased slightly, he developed slight papill-œdema and right homonymous hemianopia, and there was increasing weakness of his hemiparetic limbs.

Drainage of Loculated Abscess.—At the end of the fourth week (Aug. 9) the left parietal region was needled, a loculated collection of pus was found in the depths, and air pyograms showed that the pus was in the subdural space on the medial and inferior surfaces of the left hemisphere (Fig. 2). This pus grew a different kind of streptococcus—β-hæmolytic streptococci—and fusiform bacilli, the latter only for one day. Up to 70 c.cm. of pus were aspirated from the cavity and replaced by penicillin, and instillations of penicillin into the abscess were repeated (6,000 to 10,000 units once daily).

As the patient remained desperately ill a brain needle was eventually left in this abscess cavity and fixed to the skull by a plaster case for twenty-four hours. Systemic penicillin was resumed. No immediate effect was obtained: the patient remained comatose with moist rales in both lungs and a respiration rate of 70. After four days he began to respond, and a few days later his intracranial pressure fell to normal.

Nine days after evacuation of the subdural abscess (Aug. 18) his right hemiplegia was still practically complete and his aphasia severe; and he had visual agnosia, attempting to eat a penny in mistake for a biscuit. However, on Aug. 28 his hemiplegia was greatly improved and on Sept. 1 he began to move about in bed and to talk more freely, though still not spontaneously.

In the twelfth week (Oct. 1) he began to get up and about with some help. By then he was physically and mentally free from signs and symptoms, apart from right homonymous hemianopia, generalized debility,

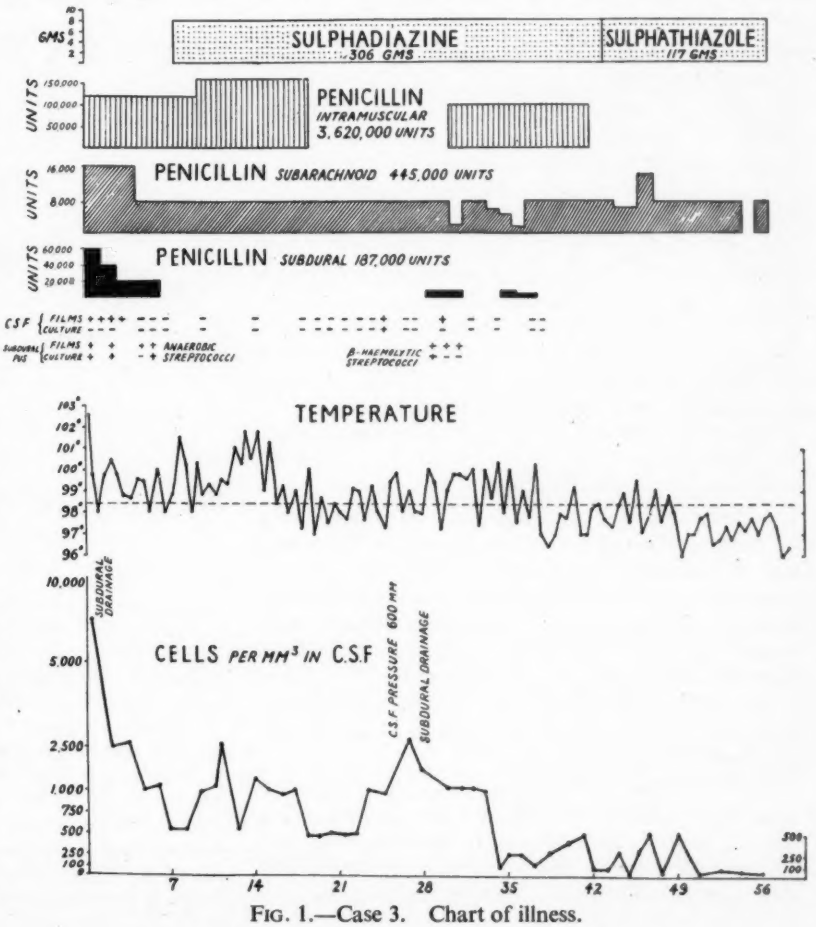


FIG. 1.—Case 3. Chart of illness.

and severe emaciation. A ventriculogram showed marked ventricular dilatation, slightly more on the left side, with no ventricular displacement (Fig. 3), thus excluding any residual loculation of pus. The cerebrospinal fluid contained 10 mg. per cent. of protein and 8 cells. The frontal osteomyelitis (Fig. 4), which had produced the pericranial abscess and had become visible in the later radiographs, subsided without operative removal of the bone. He was discharged from hospital on Oct. 13, 1944, three months after his admission, weighing 3 st. 10 lb.—a gain of 12 lb. in the previous five weeks.

Subsequent Course.—He steadily gained weight. His nose continued to discharge and was found to be obstructed by polyps, and his right antrum remained opaque. Therefore in May, 1945, Mr. G. N. Livingstone performed a right Caldwell-Luc antrostomy and removed the polyps and the anterior parts of the middle turbinate bones. The patient returned to school in September, 1945 and, apart from occasional bouts of rhinitis and a skin rash attributed to taking "Benadryl," he remained well. When last seen in August, 1947, he was making steady progress at school but had not fully caught up with his contemporaries. He had had no fits or headaches. He still had a right homonymous hemianopia which was incomplete in the lower quadrants.

In this case, although the osteomyelitis began on the right side of the frontal bone the purulent pachymeningitis affected the subdural space over the left hemisphere. Leptomeningitis was more severe in the early stage of the illness than in most of our cases and the infecting organism, an anærobic streptococcus, was found in, though not cultured from, the cerebrospinal fluid. The patient was *in extremis* for several weeks. The left frontal pachymeningitis cleared up with subdural drainage and penicillin, but three weeks later the patient became much worse, and developed papillœdema, right homonymous hemianopia, and severe rise of intracranial pressure, and a large collection of pus was found deep in the left side of the cranium, in the subdural space on the medial and inferior surfaces of the left cerebral hemisphere. After drainage of this abscess and instillation of penicillin the boy gradually recovered; and subsequently underwent antrostomy and turbinectomy with removal of polyps as a prophylactic against further attacks. Recovery from right hemiplegia was ultimately complete, and from homonymous hemianopia it was partial. The boy is left with dilated ventricles, but his intelligence, though not yet up to former standards, is reasonably good and he has had no fits.

The following case is another example of loculated subdural abscess which differs from the preceding one in having, in addition to osteomyelitis and purulent pachymeningitis, an extradural abscess and also a thrombosis of one common carotid artery.

Case 4. *Frontal sinusitis. Spreading osteomyelitis of skull. Extradural frontal abscess. Purulent pachymeningitis* (*streptococcal*). *? Thrombosis of common carotid artery. Penicillin therapy. Loculated subdural abscess and multiple operations. Recovery.* (R.I. 40019/45.)

A girl, aged 14 years, with a history of otitis media four years before, developed a cold with copious nasal discharge. Four to five weeks later she came home from work complaining of severe pain in the right supraorbital region. After a week in bed she returned to work for five days, but her pain recurred and she had to take to bed again. Ten weeks after the onset of symptoms she complained of weakness and pins and needles in her left upper and lower limbs, together with intolerable exacerbations of her frontal pain and vomiting, followed by confusion. Two days later she was sent to the Radcliffe Infirmary.

On admission, on March 4, 1945, she was confused but able to answer questions. She had a mild pyrexia (100° F.) with a pulse rate of 72 per minute, marked meningism, early papillœdema, a complete flaccid left hemiplegia, some sensory loss in the left limbs, and a left homonymous hemianopia. Blood pressure was 110/70 mm. Hg. Lumbar puncture yielded a milky cerebrospinal fluid under 300 mm. pressure, containing only 8 cells per c.mm., 120 mg. per 100 c.cm. of protein, and no organisms either on direct films or culture. Radiographs of her skull showed diffuse mottling of the frontal bone suggesting osteitis, and opacity of the right frontal sinus and right maxillary antrum. The white blood count was 19,000 per c.mm.

Treatment.—Bifrontal and right parietal burr-holes were made on March 4. In the right parietal and left frontal regions the dura was normal and the brain looked œdematous. In the right frontal region an extradural collection of pus was found. The infected dura was not opened. A rubber catheter was inserted extradurally for three-hourly injections with 6,000 to 12,000 units of penicillin for seven days. Penicillin (6,000 units) was also injected into the left ventricle; and 40,000 units were given intramuscularly at three-hourly intervals for seven days, followed by 20,000 units three-hourly for another fourteen.

There was no immediate improvement. While on the table she had numerous left sided focal epileptic attacks resulting in generalized convulsions. She became delirious and therefore, 36 hours after admission, a right frontal flap was turned and a large area of infected frontal bone—reaching from the coronal suture down to and including the roof of the right frontal sinus, which was stripped of its chronically inflamed mucosa—was rongeured away. The dura in the whole area thus exposed was covered with thick granulation tissue and with some free pus. This time the dura was incised in two places; from the anterior incision a few c.cm. of subdural pus was aspirated. Two fine rubber catheters were inserted under the dural incisions for instillation of penicillin (4,000 units three-hourly). A blood transfusion of 1 pint was given.

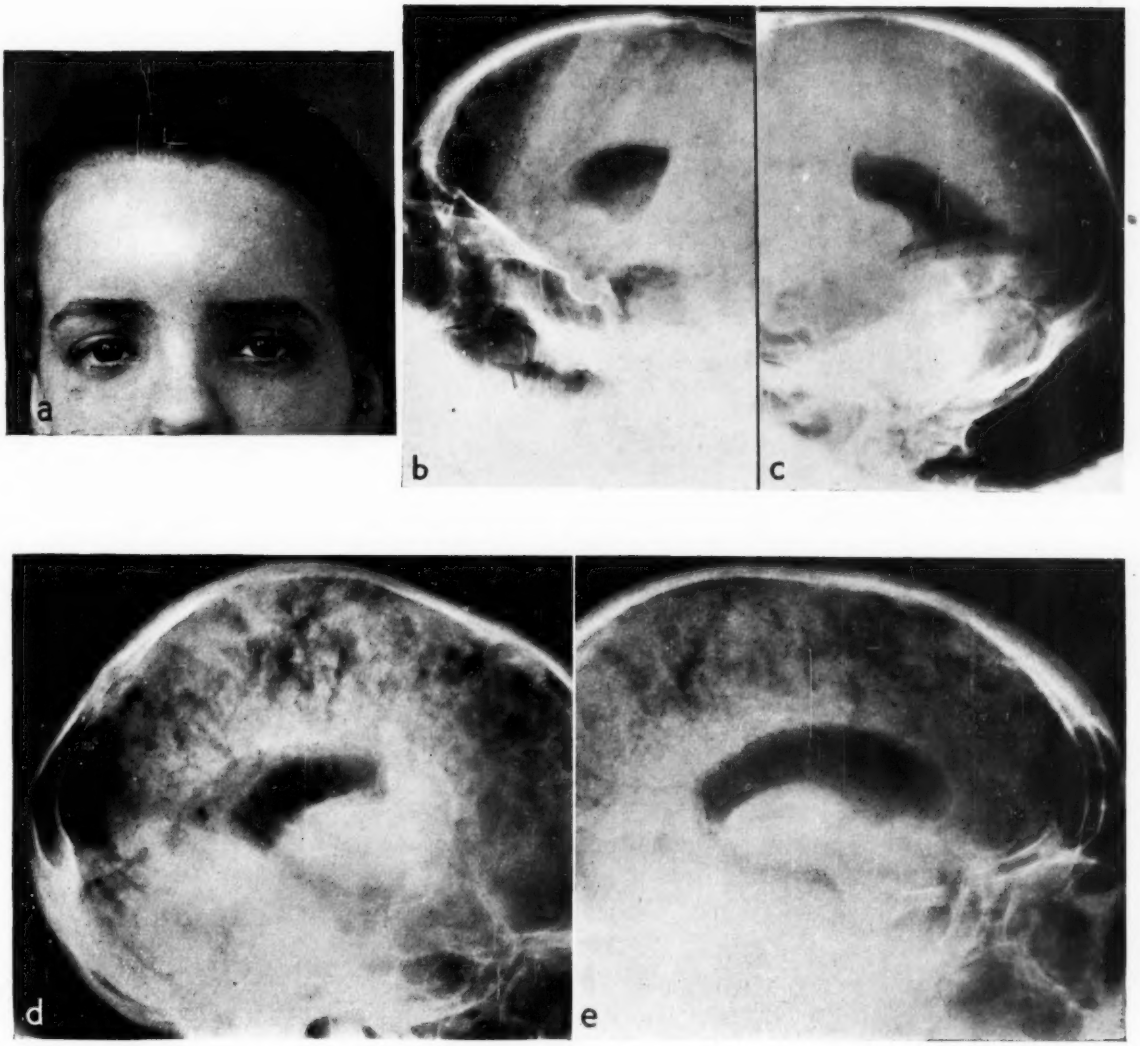


PLATE I (*a*).—Pericranial abscess of the forehead in a case of pansinusitis and chronic focal osteomyelitis of frontal bone with extradural abscess. The infected bone was excised and the abscesses drained. On the morning of operation the patient vomited, and five days after operation she became unconscious. Free subdural pus over the right hemisphere was drained, but she died sixteen days after the first operation. (L.H. 1079.)

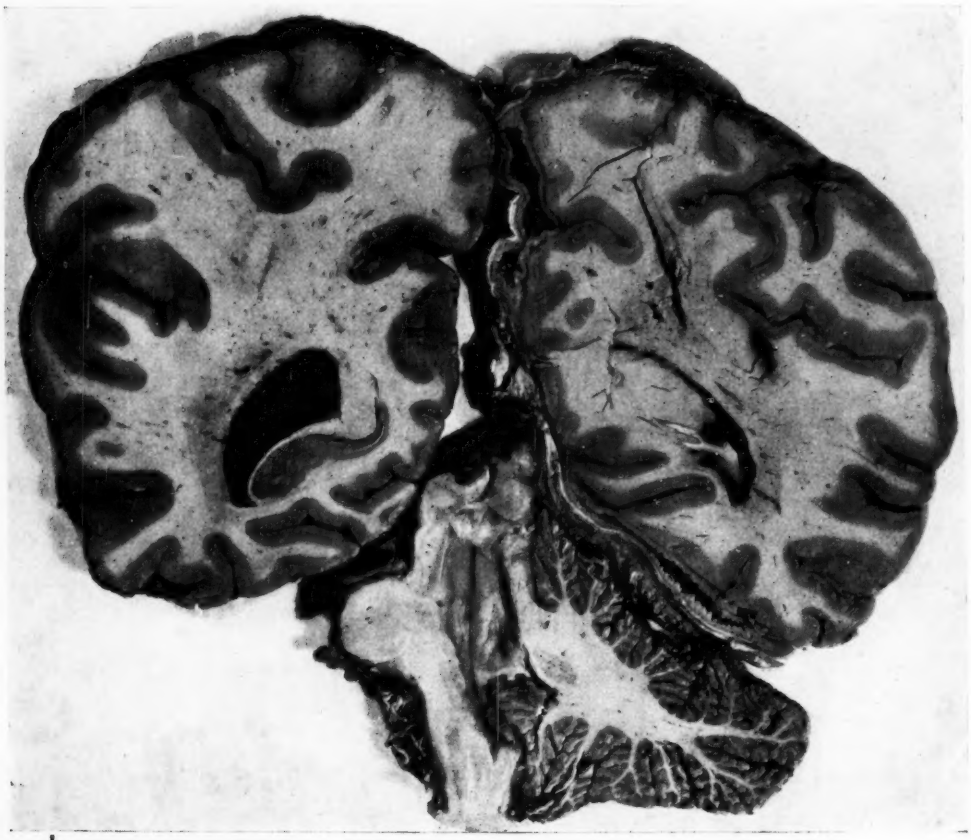
(*b*) and (*c*).—A case of head injury, with air in the subdural space (and ventricles), (*b*) face up, (*c*) face down. In (*b*) the subdural air is against the frontal bone ; in (*c*) it is seen behind the posterior horn of the lateral ventricle against the occipital bone. (R.I. 63080/46.)

(*d*) and (*e*).—A case of idiopathic epilepsy, with air in the subarachnoid space (and ventricles), (*d*) face down, (*e*) face up. The air in the ventricles moves freely with the change of posture but that in the subarachnoid space does not. (R.I. 77325/47.)

a

PLATE II (*a*).—The brain from a case of purulent pachymeningitis following pansinusitis and chronic osteomyelitis of the frontal bone. Following external drainage of the left frontal sinus the patient immediately developed signs of purulent pachymeningitis over the right cerebral hemisphere and he died thirteen days later. The figure shows dura adherent to the frontal poles, and behind that, particularly on the right side in the parasagittal region, though to some extent also on the left side, a fibrinopurulent membrane on the outer surface of the arachnoid which obscures the pattern of the underlying convolutions. Section showed also purulent leptomeningitis over the frontal lobes, thrombophlebitis, and gross old and recent softening of the underlying brain. (P.M. 31, 1930.)

(*b*).—Collapsed loculated subdural abscess on medial and inferior surfaces of right cerebral hemisphere as a sequel to purulent pachymeningitis (pneumococcal). (P.M. 234, 1943.) (By kind permission of the *Journal of Pathology and Bacteriology*.)



b

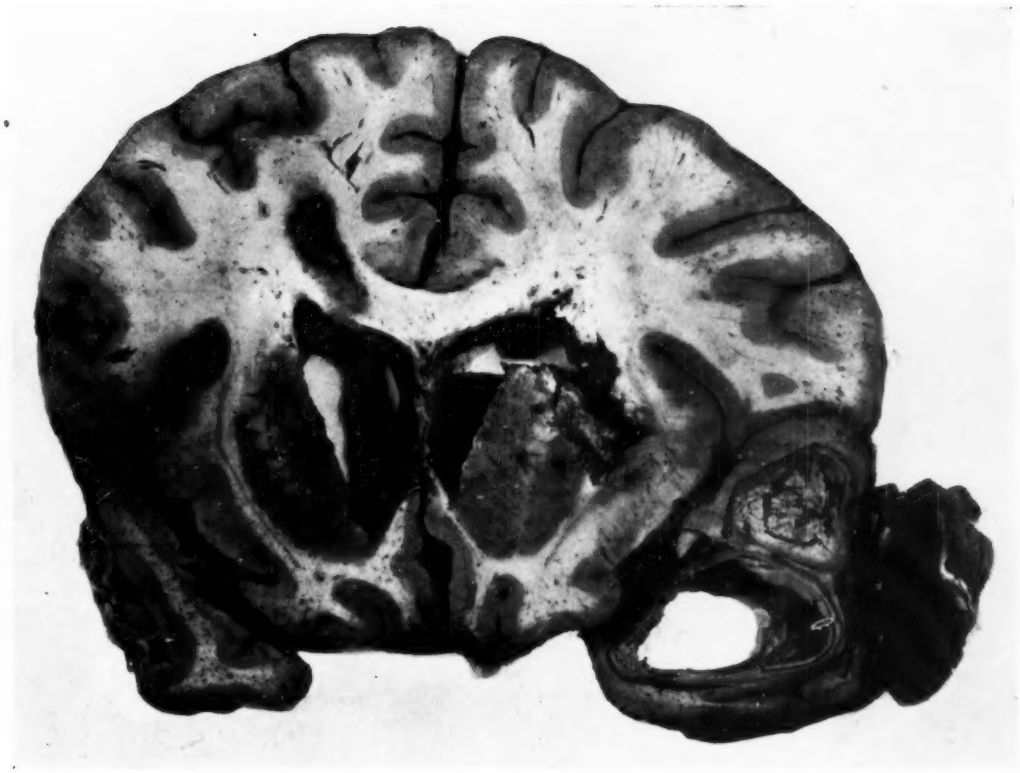


PLATE III.—Multilocular abscesses of right temporal lobe following purulent pachymeningitis and loculated subdural abscess. The patient, a man aged 27 years, had chronic pansinusitis for three years treated by multiple operations and antral washouts. He developed spreading osteomyelitis of the right superior maxilla, followed a month later by sudden onset of left hemiplegia and other signs of purulent pachymeningitis. At operation pus (culture, non-hæmolytic streptococcus) was obtained from the subdural space in the right temporal region but not in the parietal region. He was given local penicillin treatment, supplies being inadequate for full systemic treatment. He developed a brain fungus (which can be seen in the figure) and died from ventriculitis due to *E. coli*. Necropsy revealed numerous loculi of pus in the subdural space of the anterior half of the right cerebral hemisphere, maximal at its medial border ; a further subdural abscess over the lateral aspect of the *left* temporal pole ; two cerebral abscesses in the right temporal lobe (shown in the figure) beneath the site of the drained subdural pus and the brain fungus ; two abscesses in the right frontal lobe, one near and one at a distance from the temporal abscesses ; ventriculitis and purulent leptomeningitis. There were also abscesses in the right pterygoid muscles and a sequestrum in the orbital plate of the right superior maxilla. (P.M. 67, 1944.)

PLATE IV (*a*).—Case 1 : spreading osteomyelitis of the skull.

(*b*).—Case 2 : showing a rubber catheter in the subdural space, extending backwards from a frontal burr-hole to the parieto-occipital region.

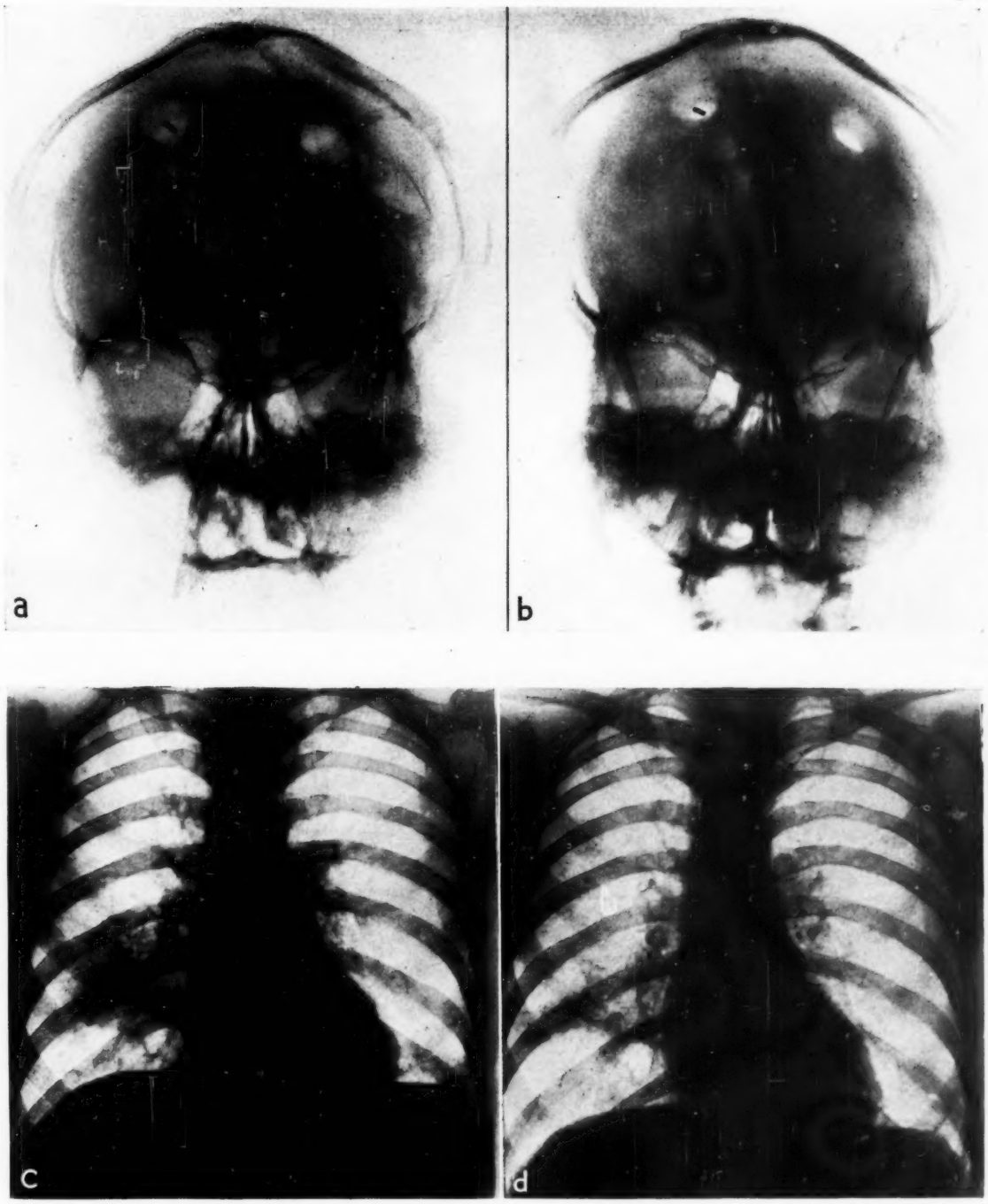


PLATE V.—Case 2: osteomyelitis of the frontal bone. (*a*) in the acute stage (showing also a catheter in the subdural space); (*b*) six months later the osteomyelitis has cleared up without surgical removal of bone; (*c*) consolidation of the right lung; (*d*) ten weeks later.

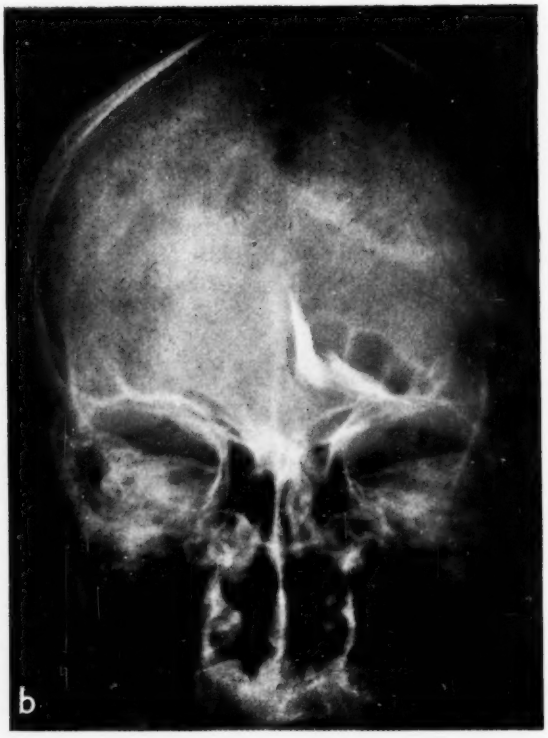


PLATE VI (*a*).—Case 4: pyogram of right subdural abscess. Note also the defect from removal of osteomyelitic bone.

(*b*) and (*c*).—Case 5: pyograms of loculated subdural abscess, (*b*) anteroposterior, and (*c*) lateral, where the thorotrast shows as an irregular ill-defined shadow above the tentorium.

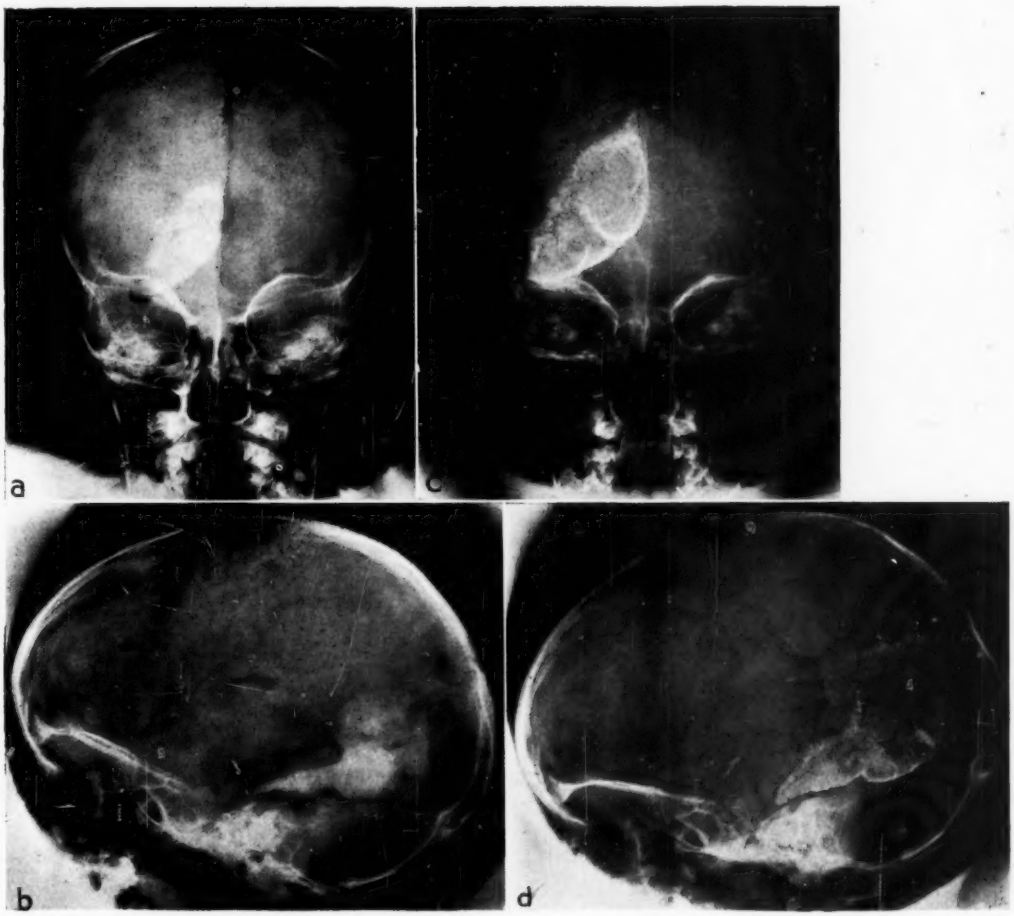


PLATE VII.—Loculated subdural abscess in a child of 3 years who had had mastoiditis followed by an abscess in the corresponding middle fossa (? subdural). When she came under our care (1944) she had a brain fungus and the subdural abscess (culture sterile) shown above. There was no hemiplegia associated with this abscess at first. At necropsy there was also a cerebral abscess beneath the fungus and pyocephalus. (*a*) and (*b*).—Immediately after injection (May 2). (*c*) and (*d*).—Four weeks later (May 31). At no time did this patient have the syndrome of purulent pachymeningitis and the case is not included in the present series. (R.I. 25501/44.)

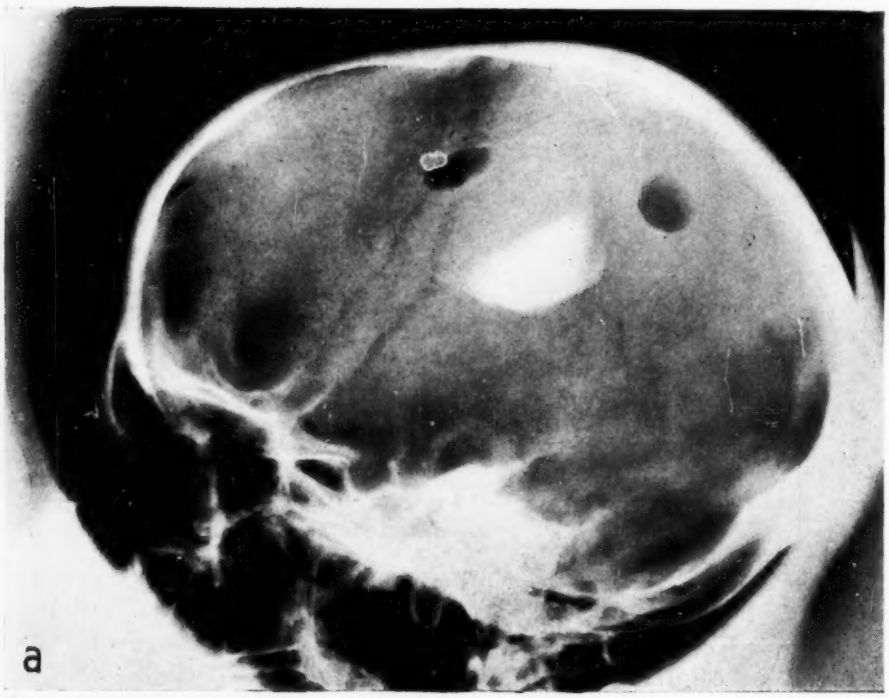
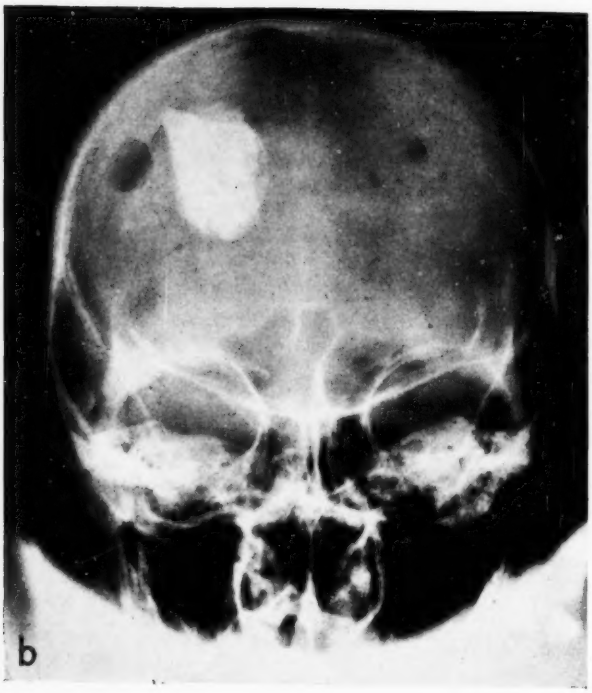


PLATE VIII (*a*) and (*b*). — Case 6: Thorotrast pyogram of cerebral abscess secondary to loculated subdural abscess.



(*c*).—Case 6: microphotograph of subdural and cerebral abscess. (i) Subdural abscess, (ii) intracerebral abscess, (iii) intervening cerebral cortex.

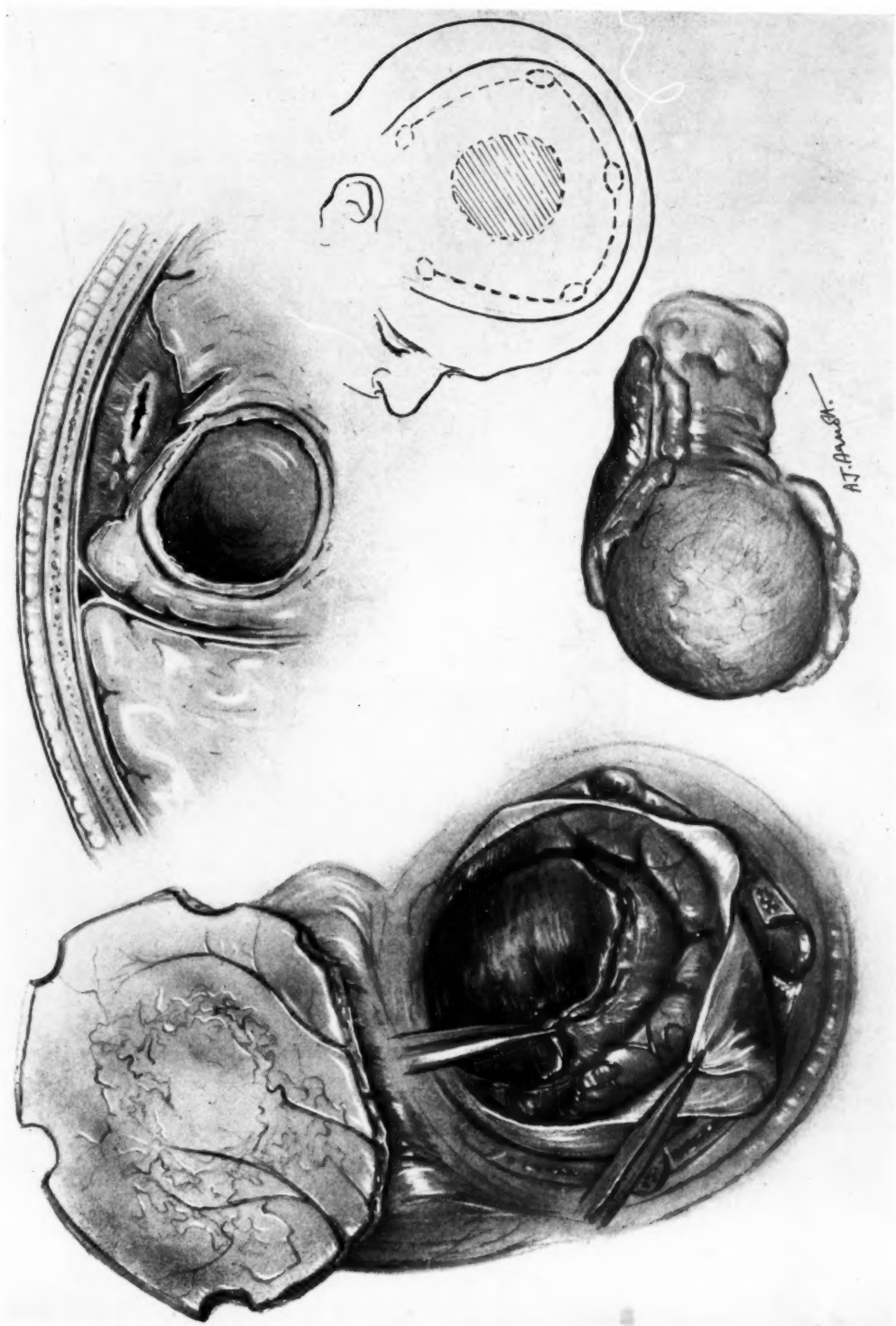


PLATE IX.—Case 6: operation sketch showing appearances of old osteomyelitis on the inner surface of the bone flap, a chronic subdural abscess with severe surrounding fibrous reaction, and an underlying cerebral abscess.

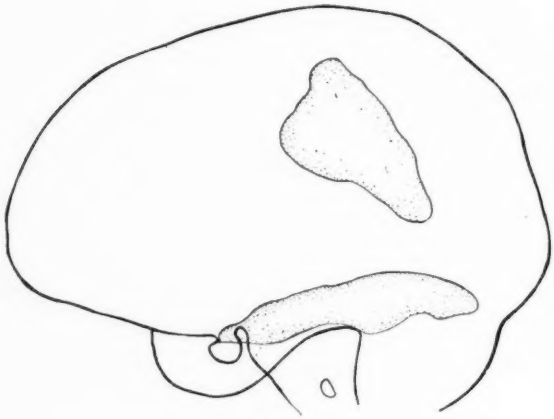


FIG. 2

FIG. 2.—Case 3. Air pyogram showing site of subdural abscess on medial and inferior surface of the left hemisphere.

FIG. 3.—Case 3. Ventriculography after recovery, showing bilateral symmetrically placed hydrocephalus. The ventricle on the affected left side is the larger.

FIG. 4.—Case 3. Tracing of radiograph, showing osteomyelitis of left frontal bone as it appeared five weeks after the onset of purulent pachymeningitis. It subsided under penicillin treatment without suppuration or removal of bone.

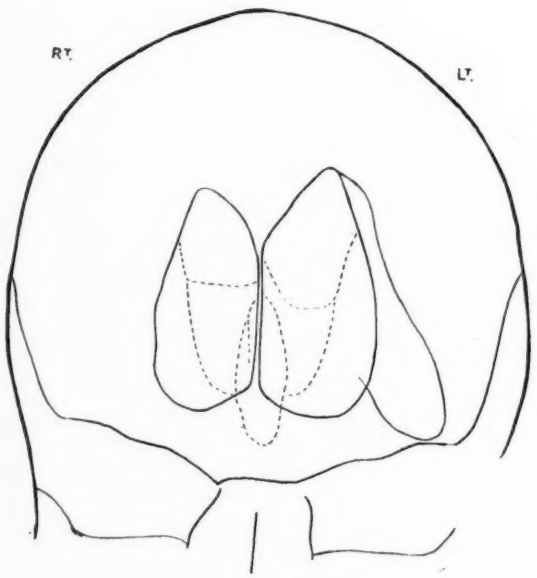


FIG. 3

FIG. 4

Bacteriology.—The organisms from the extra- and subdural pus, seen on films, but not grown in cultures, were streptococci.

Subsequent Course.—Her general physical and mental condition improved slightly. Though confused and drowsy, she recovered from her delirium and fits and became apyrexial on the sixth day ; but there was little improvement of her left hemiplegia, her hemianopia persisted, and the lumbar puncture pressure remained high (600 mm.). We concluded that she probably had a cerebral abscess. Therefore ten days after admission, on March 15, in an attempt to localize the abscess, right common carotid arteriography was done. The films showed an almost complete obstruction of the common carotid at its bifurcation : there was no filling of the internal carotid or its branches, the external carotid and its branches contained a little of the contrast medium, and there had evidently been a reflux into the subclavian for the vertebral artery was well filled (Fig. 5). This totally unexpected finding may have been due to carotid thrombosis, which could explain the hemiplegia and even the homonymous hemianopia ; but it did not explain the great rise of intracranial pressure, nor did it exclude the presence of an abscess.

On the same day (March 15) the brain was explored with a needle first in the right frontal lobe with negative result, then in the posterior part of the right parietal lobe, where at a depth of 6 cm. pus was encountered and 5 c.cm. aspirated. Penicillin (8,000 units) and thorotrast (2 c.cm.) were injected into the cavity. Radiographs showed that the contrast medium outlined the tentorium and falx, that is, that there was a loculated subdural abscess on the base and medial surface of the right occipital lobe (Plate VI a). The pus contained numerous degenerate Gram-positive cocci on films ; cultures were sterile.

On the following day the subdural abscess was approached through another small craniotomy slightly to the right and in front of the external occipital protuberance. A catheter was inserted into the abscess, allowing evacuation of a large quantity of pus, and penicillin was instilled (6,000 units, first three-hourly then six-hourly) for four days. As there was no immediate response to this treatment, another right parietal, parasagittal burr-hole was made on March 19, but no further pus was found. Her hæmoglobin had fallen to 46 per cent., so she was given two blood transfusions. On March 21 her lumbar puncture pressure fell, and from then onwards she gradually recovered. One month after admission ventriculography confirmed the disappearance of any space-occupying lesion (Figs. 6 and 7), and pressure and contents of the cerebrospinal fluid were normal. Throughout the course of her illness leptomeningitis had never been severe, nor had any bacteria been seen in her cerebrospinal fluid.

Owing to shortage of beds she was discharged to another hospital on April 6, 1945, still pale, weak, somewhat confused, and bedridden. The left hemiplegia was still virtually complete, there was severe postural loss in the left limbs, and left homonymous hemianopia. In June she was walking and able to leave hospital. In August, 1945, she showed only slight sensory and motor weakness of the left limbs. When last seen in August, 1947, she was employed in housework. Her visual fields were full, and only very slight traces of the hemiparesis could be found in the left lower limb. She had had no headaches or fits. The right carotid arteries were pulsating normally, suggesting that any obstruction there may have been had now disappeared.

In this case as in the previous one the subdural pus over the convexity of the right hemisphere was successfully dealt with by the initial instillations of penicillin into the subdural space. The patient's hemiplegia, hemianæsthesia, and homonymous hemianopia failed to improve and her intracranial pressure remained very high. A subdural abscess was subsequently found on the medial and inferior surfaces of the right hemisphere.

It will be noted that this patient had seven separate operative procedures in the course of one month : (1) drainage of extra-dural abscess ; (2) removal of osteomyelitic bone and subdural drainage ; (3) arteriography ; (4) needling of loculated subdural abscess ; (5) insertion of catheter into subdural abscess ; (6) further exploration of the subdural space ; and (7) ventriculography. In retrospect two of these operations, nos. 3 and 6, might have been dispensed with, but at the time, in view of the grave state of the patient, it seemed essential to learn more of the intracranial pathology, and neither of these operations affected the patient adversely. The point is that unless the whole of the subdural space can be adequately supplied with penicillin at the beginning, and particularly that part of it on the medial and inferior surfaces of the cerebral hemisphere, repeated operations will usually be necessary.

The infecting organism could never be cultivated but morphologically it was a streptococcus. Clinically this case showed a less intense infection than Cases 1 and 2. It differed also in the presence of a definite frontal extradural abscess which was characterized clinically by severe frontal pain. Severe localized pain was not present in uncomplicated purulent pachymeningitis and should be regarded as an indication of an associated extradural abscess.

Another point of note is that notwithstanding the fact that there was an abscess in the subdural space immediately over the calcarine fissure, and that considerable quantities of penicillin were instilled into the abscess (144,000 units in four days) the recovery from homonymous hemianopia was complete ; and there were no fits in the next two and a half years.

The carotid obstruction found on arteriography was totally unexpected and we do not know its

FIG. 5

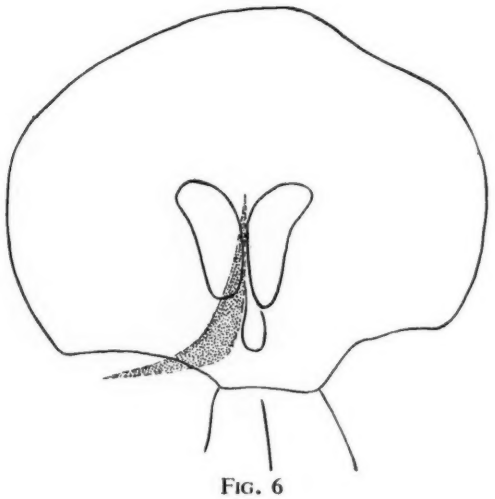


FIG. 6

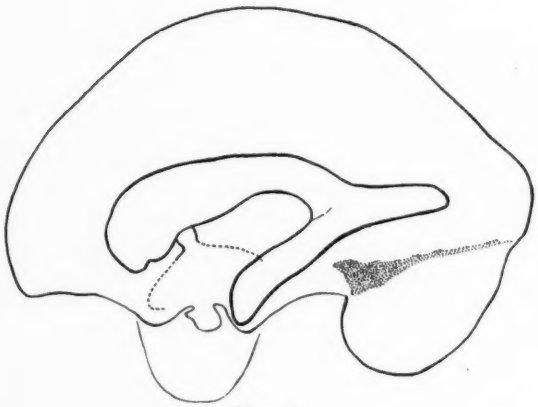


FIG. 7

FIG. 5.—Case 4. Tracing of arteriogram of the right common carotid, showing complete obstruction of internal and partial obstruction of external carotid at the level of the bifurcation. There is reflux of contrast medium into the subclavian artery with resultant filling of vertebral artery.

FIG. 6.—Ventriculogram showing symmetrical slightly dilated lateral ventricles and, indicated by a faint thorotrast shadow, the shrunken capsule of the subdural abscess.

FIG. 7.—Lateral view of ventriculogram shown in Fig. 6.

cause. It was probably not due to spasm; with our technique spasm has not been encountered, when, as in this case, the artery is successfully entered at the first puncture; and the patient's blood pressure was not high. We can only suppose that it was due to carotid thrombosis, though the patient is much younger than those described by Gilmour (1941) and Moniz (1941).

The following case is an example of purulent pachymeningitis with loculations following mastoid infection. Although one of the incompletely treated cases, it is included because it illustrates the mode of spread of subdural pus from the mastoid and the difficulties of finding and draining the pus.

Case 5. Left mastoiditis. Purulent pachymeningitis with loculation. Thrombosis of left lateral and other intracranial venous sinuses. Mastoidectomy and ligation of left internal jugular vein. Drainage of subdural pus and incomplete local penicillin therapy. Death. (No. 7699.)

A driver, aged 39, was admitted to the Military Hospital (Head Injuries), Oxford, on Jan. 15, 1944. Eight years before he had had a left incomplete mastoidectomy, and thereafter remained well until Jan. 9, 1944, when he began to have fever (up to 103·2° F.), and pain in the left ear followed by discharge of foul pus from the meatus and swelling of the old operation scar. On Jan. 13 Major Williams performed a radical mastoidectomy and found a subperiosteal abscess in contact with the lateral sinus, which apparently was not thrombosed; there was also a small extradural abscess above the tegmen.

On Jan. 15 he was drowsy and had some headache, and his temperature rose again to 103·5° F. Lumbar puncture with unilateral jugular compression showed a partial left jugular block suggesting a mural thrombus (protein 80 mg. per 100 c.cm., 100 white cells per c.mm.), and so the left internal jugular vein was tied. On the same evening he was transferred to Oxford.

On admission he was drowsy, confused, and showed slight nominal dysphasia. Temperature was 102·2° F., rising to 104°, pulse rate 108, respirations 22 per minute. To confrontation there was a partial right upper quadrantic homonymous hemianopia and he had slight right lower facial weakness and slight weakness, clumsiness, and flaccidity of the right upper limb. His mastoid wound was clean. Lumbar puncture yielded clear fluid under a pressure of 180 mm. cerebrospinal fluid protein was 70 mg. per 100 c.cm., white cells 150 per c.mm. (predominantly polymorphonuclear), films and cultures sterile. He was put on a course of sulphadiazine.

In the following days he was at times drowsy and at times complaining of severe pain in the region of the left mastoid wound and in the forehead. On Jan. 22 his aphasia was worse. Later in the day he had a rigor, with rise of temperature from 103° to 106° F., and after this he became comatose and did not move his right arm or leg. His lumbar cerebrospinal fluid was unchanged, though its pressure was now over 300 mm. Blood culture was sterile. It was thought that he had infective thrombophlebitis with purulent pachymeningitis.

Operation.—On Jan. 22 a left temporal burr-hole showed a thrombosed cortical vein, but no subdural pus on the outer aspect of the temporal lobe. However, a needle passed through the temporal lobe to the medial part of its inferior surface encountered 10 c.cm. of pus, and injection of 2 c.cm. of thorotrast at this point showed that the pus was in the subdural space alongside the falx and beneath the temporal lobe (Plate VI b and c). The thorotrast was mobile. Another small hole was now made above the left lateral sinus, the occipital lobe was retracted from the tentorium, and a further 10 c.cm. of pus was obtained. A catheter was laid in the abscess area for instillations of penicillin (3 c.cm. of solution, 500 units per c.cm. at eight-hourly intervals). Owing to shortage of supplies no penicillin could be given systemically.

Bacteriology.—The subdural pus showed pus cells and intra-cellular Gram-positive cocci on films; ærobic cultures were sterile, but anærobic cultures grew a short-chained streptococcus.

Subsequent Course.—The patient improved for three days, regaining some power in his right limbs, but on Jan. 26 he suddenly became unconscious and showed a dilated fixed pupil on the left side and extensor rigidity of the right limbs. A burr-hole was made over the left parietal lobe alongside the sagittal sinus but the subdural space there contained no pus. The site of the subdural drain was also explored again, but only a small amount of pus was found. The left temporal lobe was also explored by brain needle without disclosing any abscess. The patient died on Jan. 28.

Necropsy (P.M. 53, 1944).—*Macroscopic.*—A few old pleural adhesions; patchy bronchopneumonia of the lower lobes of both lungs; slightly enlarged septic spleen, and fatty degeneration of the liver. The left jugular vein contained an infected thrombus extending down to within 1 cm. of the site of ligature. Most of the anterior part of the left petrous temporal bone showed osteomyelitis, but there was no naked-eye evidence of osteomyelitis in other parts of the skull. There were infected thrombi attached to the walls of the left sigmoid sinus (1·7 cm. by 0·5 cm.), the left lateral sinus (1 cm. long), and the sagittal sinus (one 2 cm. long in the posterior parietal region, another 0·6 cm. diameter at the Rolandic level). There were patches of friable red and grey clot lightly adherent to the walls of the torcular and the adjacent 1 cm. of the straight sinus, and red clot, probably ante-mortem, in the posterior intercavernous sinus. The left Rolandic vein was partly occluded by yellow thrombus at a point 6 cm. from sagittal sinus.

In the subdural space a layer of thick pus coated the whole of the left side of the falx and the upper surface of the left side of the tentorium, and extended over the anterior half of the convex surface of the left cerebral hemisphere, the left frontal pole, and the posterior third of the inferior surface of the left frontal lobe. A similar layer of pus covered the central 9 cm. of the right side of the falx. Beneath the pus the brain was covered by a

shaggy film of fibrino-purulent membrane and was irregularly indented. On the left side the subdural collection formed two main pockets on the medial aspect of the hemisphere, one parietal (5·5 cm. by 5·5 cm. by up to 1·5 cm. deep), the other frontal (5·5 cm. from before back by 3 cm. from above down by up to 1 cm. deep). On the right side there was a pocket of pus on the medial side of the parietal lobe (8·5 cm. from before back by 5 cm. from above down by 0·5 cm. deep). There was a further pocket of pus at the left frontal pole (3 cm. by 2·2 cm. by 1 cm. deep). In places at the margins of the pockets the dura was lightly adherent to the leptomeninges. The only signs of leptomeningitis were yellow opacity of the arachnoid over the floor of the third ventricle and faint milky opacity of the cisterna magna.

The convolutions of the convex surface of the left hemisphere were broad and flattened. There was severe symmetrical downward herniation of both hippocampal gyri, with lateral compression of the brain stem and narrowing of the aqueduct of Sylvius, and moderate herniation of the cerebellar tonsils. The left lateral ventricle was compressed, the right of normal size. There were fragments of clot in left lateral and fourth ventricles and a recent hæmorrhage (0·2 cm. diameter) in left pulvinar.

Microscopic.—Organized clot was seen in the left sigmoid and in the sagittal sinus ; in the former were a few, in the latter abundant Gram-positive cocci, many of them within the cytoplasm of phagocytes.

Over the left parietal lobe the dura showed laminated thrombus in the larger meningeal veins. Between the dura and arachnoid there was a thick coat of degenerating leucocytes containing small clumps of Gram-positive cocci ; in the thickened leptomeninges there was great proliferative activity and much fibrin, but no bacteria. The subjacent cortex showed similar reaction, and there was degeneration of the cortical cells.

The left Rolandic vein contained unorganized thrombus, and there was a moderate inflammatory reaction in the adjacent meninges but no gross abnormality of the surrounding cortex.

This case is an example of the difficult group in which infection of the subdural spaces arises from the petrous bone and is associated with thrombosis of the lateral sinus. Notwithstanding surgical treatment of the mastoid within one week of the onset of acute symptoms, the subdural space became infected. Aphasia and homonymous hemianopia were the first symptoms. Subdural pus was found on needling the temporal lobe, and might easily have been diagnosed as a cerebral abscess but for the characteristic appearance of the thorotrast pictures (Plate VI b and c). The subdural pus was not fully drained ; nor was the subdural space adequately irrigated with penicillin solution. When three days later the patient suddenly became worse, a search for subdural loculi was made in the usual place, but none was found. This indicates the difficulty of exploring the subdural space, alongside the falx. After death, which was due to the severe rise of intracranial pressure, it was found that the pus had spread widely in the subdural space, not only on the side of the original lesion but also over the opposite hemisphere. The order of spread was from the inferior surface of the left temporal lobe to the left side of the falx ; then to the inferior surface of the left frontal lobe and to the right side of the falx. The convexity of the brain escaped, except at the left frontal pole.

The part played by thrombosis of the large venous sinuses was at the time difficult to assess ; in retrospect there can be little doubt that in such cases there should be a direct surgical attack upon the clot. In this case matters were made more difficult by the fact that at the time penicillin was in short supply and there was only enough available for local instillations into the subdural space. These were given at too infrequent intervals in view of what we have since learned about penicillin in the subdural space.

Diagnosis of Loculated Subdural Abscess.—In our fifteen cases of purulent pachymeningitis treated by penicillin there have been nine cases of loculated subdural abscess (Tables VI and VII). Three of these were associated with cerebral abscess and will be considered more fully in the next section. Of the other six, five were verified by operation and pyography (subsequently confirmed by necropsy in three cases). In the remaining case the lesion was suspected on clinical grounds and on the ventriculographic and arteriographic appearances, but the symptoms subsided during prolonged systemic treatment with penicillin and so it was not verified.

Whether secondary to paranasal sinus or to mastoid disease, the favourite site for subdural loculation was alongside the posterior half of the falx and on the adjacent tentorium of one or both sides, though loculation could also occur on the convexity (Case 6). If unilateral the abscess was usually on the side of the original purulent pachymeningitis, though not invariably (Plate II b).

There may be more than one loculus, but multiple loculi are usually in continuity. The symptoms produced by loculated abscess were most commonly a recurrence of the initial sensori-motor hemiplegia with homonymous hemianopia in the second to fifth week after first drainage of subdural pus ; or the hemiplegia failed to improve after the initial treatment of the purulent pachymeningitis. Thus, the loculus does not usually produce new localizing signs. Intracranial pressure as measured by lumbar puncture steadily increased to levels of 600 mm. of water or more, and there were other signs of raised pressure : papillœdema, increasing drowsiness, and

deterioration of the patient's general condition. On this basis further surgical explorations were undertaken.

These symptoms were probably kept in check to some extent by continued systemic penicillin, for in three cases they only became evident after penicillin was stopped, and in three other cases the symptoms were entirely suppressed by penicillin, though in two of these the patient subsequently developed a cerebral abscess. The common loculated subdural abscess alongside the falx produced a characteristic deformity of the ventricles (Figs. 8a and b and 9b and c), and arteriograms in one probable case showed localized depression of the calloso-marginal vessels (Fig. 9a). However, the diagnosis can only be made with certainty in life by thorotrast or air pyograms after needling and aspiration of the abscess (Figs. 2 and 8c and d ; and Plates VI a, b, c, and VII). The appearances are characteristic : in the antero-posterior view the medial and inferior borders of the thorotrast shadow correspond to the falx and tentorium ; in the lateral projection the upper surface of the tentorium is sometimes outlined, but otherwise the thorotrast shadow assumes bizarre shapes. After a few days the thorotrast is taken up by the macrophages of the abscess wall, and eventually in radiographs is seen to have a strikingly crenated outline (Plate VII ; also Tutton and Shepherd, 1948).

Before we realized the true nature of this condition we thought when we encountered pus in these cases after needling deeply in the parietal lobe that we were dealing with an abscess deep in the brain substance, or pyocephalus of the lateral ventricle. And when the patient failed to improve we continued to search by needle for intracerebral collections. But the pyograms of subdural abscess are unmistakable, since the abscess is outlined medially and inferiorly by the falx and tentorium. The site of the abscess seems to be approximately the same in the cases arising from mastoid infection as in those from infection of the paranasal sinuses. It is important to realize that loculated subdural abscess can arise in this situation not only as a result of purulent pachymeningitis, but also as a sequel to brain abscess (Plate VII).

With systemic penicillin therapy small subdural loculations may not give rise to complete hemiplegia and may escape notice in patients about to be discharged from hospital as apparently cured, unless ventriculography is performed in such cases as a routine before discharge.

Subdural Loculation with Delayed Cerebral Abscess.—This condition can best be described by the following case report.

Case 6. *Perforation of pelvic colon. General peritonitis followed by pelvic abscess. Osteomyelitis of skull and pericranial abscess followed by symptoms of purulent pachymeningitis ; relieved by systemic penicillin. Recurrence of symptoms four weeks after cessation of penicillin treatment. Operative removal of old subdural abscess and cerebral abscess* (*Streptococcus viridans*). *Recovery, with severe residual symptoms.* (R.I. 70609, 1947.)

A woman aged 45 developed generalized peritonitis on Oct. 25, 1946, due to perforation of the pelvic colon by a hare bone. She was treated within a few hours by peritoneal drainage and temporary cæcostomy. During November a large pelvic abscess developed : it was drained suprapubically, and it also discharged through the rectum and vagina. She did well and left hospital on Dec. 27, 1946. On Jan. 1, 1947, she developed severe headache, stiff neck, and rigors. A swelling formed on the right side of the head and she was readmitted to hospital on Jan. 4, when she was found to have a fluctuant swelling in the right fronto-parietal region, left facial weakness, dullness and crepitations at the base of the right lung, and some pelvic tenderness. Lumbar puncture gave cerebrospinal fluid containing 10 lymphocytes per c.mm. and 160 mg. of protein per 100 c.cm.

She was treated with systemic penicillin (50,000 units three-hourly until Jan. 16) and, on Jan. 8, 5 c.cm. of pus was aspirated from the swelling on the head : non-hæmolytic streptococcus and *Staphylococcus albus* were cultured. On Jan. 9 the patient had weakness of the left upper limb and left side of the face, which gradually increased. On Jan. 12 she had several epileptic attacks, after which her hemiplegia was complete. During the next ten days the hemiplegia improved slowly. On Jan. 25 the frontal swelling recurred, she became drowsy and incontinent of urine and fæces, and her optic discs were slightly swollen ; systemic penicillin was resumed and 5 c.cm. of pus was again aspirated from the frontal swelling. During February her symptoms cleared up and she was discharged from hospital on March 1. Her lumbar cerebrospinal fluid remained unchanged apart from an increase of its resting pressure.

She remained well for about four weeks and then once more developed weakness of the left arm and leg which became complete within a few days. She became apathetic and confused and was admitted to the Radcliffe Infirmary on April 9.

On admission the patient was stuporous and incontinent but her general condition was good. Temperature was normal, pulse rate 80 per minute. Her neck was moderately stiff and Kernig's test was slightly positive. There was slight papillœdema, inattention in the left homonymous visual fields, and flaccid left hemiplegia, complete in the upper limb, almost complete in the lower limb, with increased tendon jerks and an extensor plantar response on the left side. The lumbar cerebrospinal fluid had a pressure of over 300 mm., and contained 130 mg. of protein per 100 c.cm., and 26 white cells per c.mm. Radiographs showed an area of osteitis in the right frontal region, but her scalp was now healthy. It was thought that she was not sufficiently

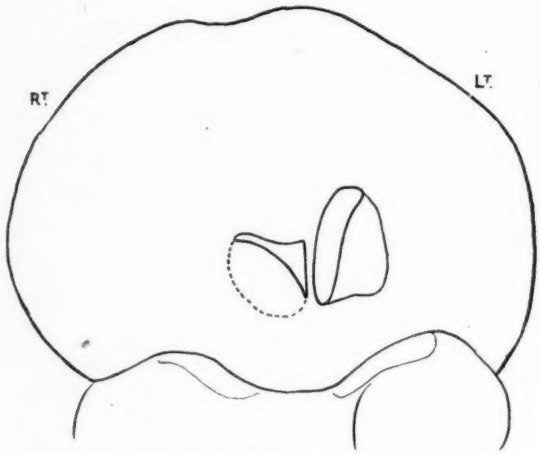


FIG. 8a

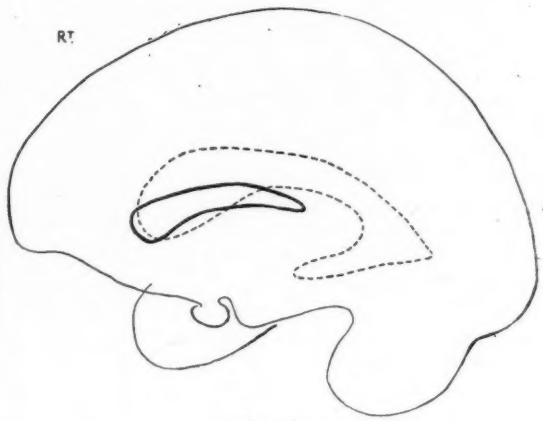


FIG. 8b

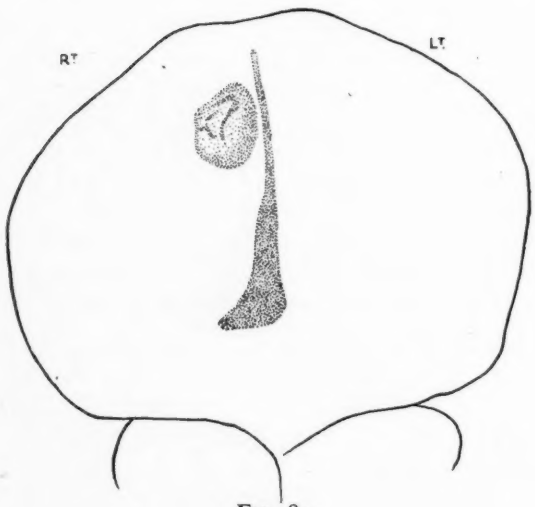


FIG. 8c

FIG. 8d

FIG. 8 a–d.—Ventriculograms and pyograms of a proved case of loculated subdural abscess after purulent pachymeningitis. The brain of this case is shown in Plate II (*b*).

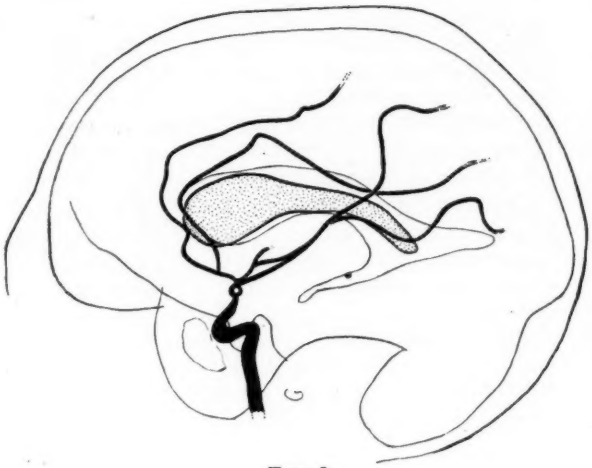


FIG. 9a

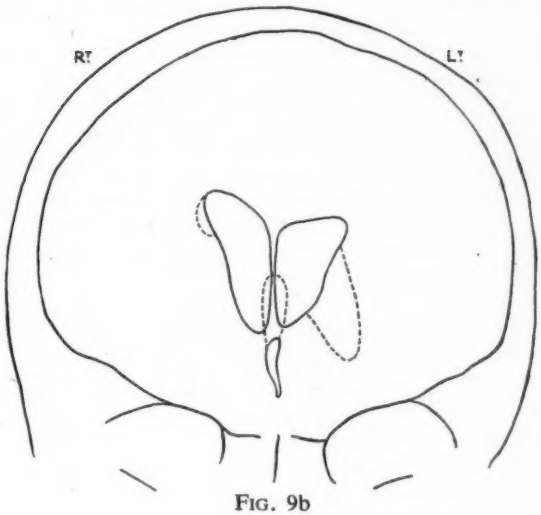


FIG. 9b

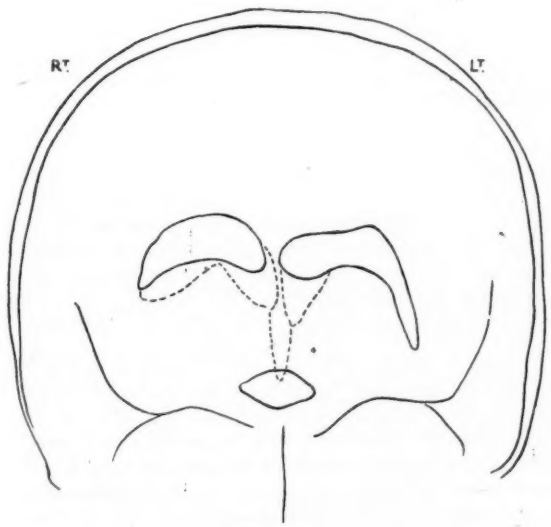


FIG. 9c

FIG. 9 a–c.—Tracings of encephalogram and arteriogram of an unverified case of a small loculated subdural abscess on the medial surface of the left cerebral hemisphere. The body of the left lateral ventricle and the adjacent left pericallosal artery are depressed from above. The ventricular system is only slightly displaced to the right, indicating that the collection is a small one. (R.I. 67032.)

ill for a subdural abscess and that she probably had an intracerebral abscess. She was given systemic penicillin 250,000 to 400,000 units daily.

Angiography showed depression of the right middle cerebral artery and displacement of the right anterior cerebral artery to the left, appearances which indicated an expanding right frontal lesion.

On April 10, through a burr-hole at the right parietal eminence, an abscess was encountered in a forward direction in the frontal lobe: 40 c.cm. of pus were removed and 100,000 units of penicillin and 3 c.cm. of thorotrast injected (Plate VIII a and b). *Streptococcus viridans* were found in films and culture.

After this operation she regained consciousness and was found to have left homonymous hemianopia, inability to follow with her eyes an object moving to the left, and gross impairment of postural sensibility in the left limbs. Her left limbs were still very weak and now spastic. She was also emotionally labile, unduly euphoric, and still incontinent. On April 25, as the abscess had increased in size, as shown by radiographs, it was tapped again: 20 c.cm. of pus were aspirated. Films showed no organisms, and culture was sterile.

On April 29, 1947, the abscess was removed through an osteoplastic flap (Plate IX). The parietal bone showed evidence of old osteomyelitis. In the subdural space there was a tough membrane, up to 0·9 cm. thick, covering the whole of the area of exploration and densely adherent to the overlying dura and to the cortex beneath. This membrane contained in the central part of the exposed field a localized, collapsed, slit-like abscess cavity (2·0 by 0·3 cm.). The brain abscess lay in the subjacent cortex but somewhat eccentrically placed in relation to the subdural abscess and not communicating with it (Plate VIII c). The brain abscess measured about 6 cm. in diameter; its capsule was firm, but not as thick as that of the subdural abscess. The subdural abscess was also removed, but much of the subdural membrane over the peripheral part of the exposed brain was not disturbed because of its dense adherence to the subjacent cortex.

After this operation the patient was increasingly drowsy, so next day the wound was reopened and a small amount of clot removed, scarcely enough to account for her symptoms. On May 4 she suddenly became more alert and thereafter made a satisfactory recovery. At the time of her transfer to another hospital on May 14 her wound was healed and her general condition good, but her homonymous hemianopia and hemiplegia were still almost complete, and she was still emotionally labile and incontinent of urine. When last seen in August, 1947, she was walking but otherwise her hemiplegia had not improved, and she had had one fit.

In this case the sequence of events and the findings at operation leave little doubt that this patient had purulent pachymeningitis soon after she developed osteomyelitis of the skull. With systemic penicillin, and without any operative treatment other than aspiration of subgaleal pus, her hemiplegia recovered and she was free from symptoms for four weeks, when she developed a brain abscess. At operation the remains of the purulent pachymeningitis were seen in the form of a thick opaque membrane or granuloma, densely adherent to the dura and to the underlying cortex, and in the centre of this mass was a collapsed abscess cavity. The brain abscess was adjacent to the subdural abscess but did not communicate with it.

It is probable that the brain abscess arose after the purulent pachymeningitis and as a sequel to it, for when she came under our care the only active source of infection found outside the brain was the very chronic collapsed abscess in the subdural space. The case illustrates the difficulties and dangers of suppressive treatment of purulent pachymeningitis with penicillin.

The following case emphasizes the same dangers and also indicates the need for obtaining ventriculographic proof that the patient is free from a space-occupying lesion before discharging him from hospital.

Case 7. Ethmoidal sinusitis and frontal osteomyelitis. Left frontal extradural, right frontal subdural collection of pus (anærobic streptococcus). Drainage of both collections. Satisfactory progress under prolonged penicillin treatment. Sudden death from left frontal cerebral abscess five months after onset. (R.I. No. 57342/46.)

A boy, aged 12 years, was admitted to the Radcliffe Infirmary on May 1, 1946, with no other history than having struck his head against a tractor two days before. From then onwards he complained of pain in his left temple. On the following day he had a number of right-sided focal epileptic attacks and developed signs of meningitis.

On admission he was conscious but obviously suffering from intolerable headache. Temperature and pulse rate were raised, and meningism was present. Both temporal regions were œdematous, and he had a little trismus, mild papillœdema, and slight left-sided hemiparesis. Radiographs of the skull showed only opaque ethmoidal air cells. The lumbar cerebrospinal fluid was under 260 mm. pressure, contained 27 cells per c.mm., and 35 mg. of protein per 100 c.cm. and was sterile.

Burr-holes revealed a subdural collection of pus confined to the right frontal lobe and the presence of extradural pus in the left frontal region; the left subdural space was not explored. Two rubber tubes were inserted into the right frontal subdural space, and one into the left extradural space, and he had 8,000 units of penicillin given through each tube at four- or five-hourly intervals for nine consecutive days; that is, 270,000 units intradurally, and 13,000 units extradurally. He also had 240,000 units of intramuscular penicillin daily for four weeks (6,720,000 units), and a daily dose of 6 g. of sulphadiazine for 25 days (150 g.). The organism found both in the subdural and in the extradural pus was an anærobic streptococcus.

He made a rapid recovery, but on May 14 he had a peculiar attack of vomiting, incontinence, headache, and pallor, possibly an epileptiform manifestation. After this he was noticed to have developed papillœdema and some weakness on the right side, whereas his original slight left-sided hemiparesis had subsided by that time. Four weeks after admission a cisternal encephalogram was performed which showed small, non-displaced ventricles. Penicillin treatment was then stopped.

By June 15 his bifrontal burr-hole wounds had not quite healed, in fact there was by now an increasing purulent discharge, growing anærobic streptococci and *Staphylococcus aureus*. He had another attack, this time with profound and protracted stupor, followed by a series of right-sided focal epileptic attacks. His wounds were excised, and only now he was found to have frontal osteomyelitis. The macroscopically diseased areas around the burr-holes were removed. The dura was opened and the subdural space on the left side was found to be obliterated by granulation tissue. He was again put on systemic penicillin after a gap of nineteen days (240,000 units in 24 hours), and this was continued for a further nine weeks. At the time of his discharge from hospital he had received 22·320 mega units of penicillin systemically.

He returned to his home on Aug. 20, three months and twenty days after his admission, all sinuses having healed, and without radiological evidence of osteomyelitis, and perfectly fit as it seemed. He had been apyrexial ever since the third week following the onset of symptoms, and we regarded the result as very satisfactory and the prognosis as good.

Six weeks after his discharge, however, we were informed that he had died at another hospital following a short illness, slightly over five months after his first symptoms. An autopsy revealed a fairly well-encapsulated abscess, the size of a large walnut, situated in the left frontal lobe.

In the absence of full information about the necropsy it is not certain that this patient had a suppressed loculated subdural abscess over the left frontal lobe; nevertheless the course of events suggests that this is probable. Two weeks after his right subdural and left extradural abscesses were treated he developed signs of a left hemisphere lesion. A cisternal encephalogram showed normal ventricles, which is a point more in favour of an early subdural abscess than of a cerebral abscess. One month later, because of further signs of a left hemisphere lesion, the dura over the left hemisphere was opened for the first time and the subdural space was found to be occupied by granulation tissue. His symptoms subsided with prolonged penicillin therapy, but six weeks after this ceased he died suddenly of a left frontal cerebral abscess.

Whether our interpretation of the pathological events is correct, or whether this boy had a left frontal abscess almost from the start, the case shows clearly the dangerous suppressive effect which penicillin may exert on incompletely diagnosed intracranial infection. Such treatment should be controlled by accurate diagnosis of the intracranial pathology, and this can be achieved only by repeated ventriculography.

Summary of Results

The results of treatment (Tables VI and VII) show that only the patients who received adequate penicillin therapy by systemic and subdural routes recovered. Seven of the ten fully treated cases recovered, but three of these had loculated subdural abscess and one other had subdural abscess and cerebral abscess within a few weeks of the onset of purulent pachymeningitis. Thus, treatment is far from being a simple matter.

One of the seven survivors, a soldier from overseas, was observed for only three months after all trace of infection had subsided. The remaining six have been observed for periods of six months to four years from the time of recovery from the acute symptoms. In five of the six signs of cortical paralysis of one hemisphere had been complete, in one incomplete. In five of the six recovery from hemiplegia and sensory loss was virtually complete. Recovery from homonymous hemianopia was complete in four, incomplete in two. In the four patients who had aphasia, recovery of speech was complete.

Infrequent fits occurred some months after the acute stage in four of the six patients; these seem to have been controlled by phenobarbitone. Recovery of intellectual function appeared to be fairly good, and all six patients were at work when last heard from; however, in the case of the schoolboy (Case 3) it is doubtful whether intellectual recovery was up to the level of his previous standard.

Ventriculography, which was done after recovery in four of the six patients, showed some dilatation of the lateral ventricles (Fig. 3), and in one case comparison with a previous ventriculogram taken in the acute stage showed that the dilatation had taken place fairly rapidly during the course of the disease.

Treatment.—Table VIII summarizes the treatment given in the ten cases for which adequate supplies of penicillin were available. Although seven of our patients recovered we are far from feeling that our methods of treatment have reached finality.

Early Diagnosis.—Early recognition and treatment of purulent pachymeningitis is clearly of first importance. For anyone familiar with the syndrome produced by the disease, diagnosis should not be difficult. In any case of doubt, exploratory

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burr-holes should be made, several if necessary, and the subdural space should be carefully examined, by depressing the brain, for the presence of pus. The associated lesions, including extradural abscess, cerebral abscess, and purulent thrombosis of the venous sinuses, may not be so easy to recognize clinically; where doubt exists the appropriate exploration should be made, and ventriculography and arteriography should be employed as required.

When there is an extradural abscess the surgeon may be faced with the problem, should he open the dura through an infected field? In the past we avoided doing this, but now with the aid of penicillin the risks of setting up leptomeningitis or other intradural infection are small. It must be very rare, if indeed it ever happens, that extradural abscess causes complete sensori-motor hemiplegia, homonymous hemianopia, and aphasia. If such symptoms exist, operative exploration should not stop short at emptying an extradural abscess; the subdural space should also be examined by opening the dura, if necessary through an infected field; in that case coarse contamination of the intradural structures should be reduced to a minimum, penicillin should be applied at the site of the dural opening, and a prophylactic dose of penicillin should be injected into the lateral ventricle or lumbar subarachnoid space.

Systemic Penicillin.—All the bacteria so far encountered have been of groups sensitive to penicillin, and intensive systemic penicillin therapy should be begun without waiting for operative proof of the presence of infection, for our most

TABLE VIII

SUMMARY OF TREATMENT IN TEN FULLY TREATED CASES

Case No. in text and year	Total penicillin given								No. of operations	Result	Remarks
	Systemic M.U.	Days	Subdural M.U.	Days	Into C.S.F. M.U.	Days	Other route	Days			
2 1943	1·8 0·7	18 9	0·153 ..	14 ..	0·16 ..	16 ..	Local sinus	.. ..	2 ..	Recovered	..
5848 1943	2·77	20	0·045	8	0·032	8	..	..	2	Died	P.M. 234, 1943
7048 1943	2·025 0·675	21 5	.. ..	.. ..	0·0075 ..	4 ..	Local sinus 0·0035	.. ..	3 ..	Recovered	..
3 1944	1·08 1·44 1·10	9 9 11	0·140 0·047 ..	6 6 ..	0·445	54	.. .. ..	.. .. ..	4	Recovered	..
4 1945	2·24 2·24	7 14	0·448 0·216	7 6	0·153 ..	21 ..	0·224 extra-dural	7 ..	.. 7	Recovered	..
62110 1946	1·44 12·00 0·48 1·92	6 25 2 4	0·448	14	0·158	15	.. ..	.. ..	4	Died	Osteoplastic flap for removal of abscess
7 1946	6·72 6·24 9·28	28 26 29	0·216	9	.. .. ..	.. .. ..	0·216 extra-dural	9	4	Died	..
6 1947	? (elsewhere) 7·44	31	..	..	..	..	..	..	3	Recovered	Subdural abscess removed with cerebral abscess
66643 1946	12·48 6·72	26 28	0·352 ..	11 ..	0·20 ..	1 ..	.. ..	.. ..	4 ..	Recovered	..
67032 1947	24·48	51	0·448	14	0·472	46	..	..	5	Recovered	..

recent cases suggest that when penicillin is given promptly the disease is somewhat milder. As our experience has grown we have increased both the dose and the duration of systemic penicillin (Table VIII) and we now recommend not less than 100,000 units three-hourly, at least until the organism has been identified and its *in-vitro* sensitivity to penicillin estimated. Even larger doses might be required if the organism proved to be relatively resistant ; and, indeed, it is clearly an advantage to maintain a high level of penicillin in all parts of the subdural space from the earliest possible moment. Systemic penicillin should be continued for at least eight weeks if there is osteomyelitis of the skull or facial bones, if purulent thrombosis of the venous sinuses is suspected, or if there is any suspicion of the formation of a loculated subdural abscess.

The patient should be under close medical observation at the time when penicillin is stopped and for the next four to six weeks, in order that recrudescence of infection in the subdural space, in the brain, or in the skull may be promptly recognized and treated.

Subdural Penicillin.—Theoretically it might be possible in the early stage of purulent pachymeningitis to treat the infection of the subdural space with massive doses of systemic penicillin (200,000 units two-hourly), with the object of obtaining high levels of penicillin in all parts of the subdural space. The experience of Case 6 does not favour the experiment, but the amount of penicillin administered in the early stage was probably no more than standard dosage for the general run of pyogenic infections. Once the subdural suppuration is established even massive doses of penicillin may not eradicate the infection: Case 7, who had 22 mega units systemically in thirteen weeks, died of a cerebral abscess six weeks after penicillin was stopped.

Penicillin solution by the subdural route probably has the advantage of acting mechanically as well as by providing a high level of penicillin. In our most successful case (Case 2) very large quantities of dilute penicillin solution were injected into the subdural space for fourteen days and the infection cleared up without subdural loculation or any other complication. The in-dwelling subdural catheters should be spread as widely as possible over the convex surface of the cerebral hemisphere and their position should subsequently be ascertained by radiographs (Plate IV b). If they are not satisfactorily placed they can be altered by manipulation, or additional tubes can be inserted at a further operation. As much penicillin solution as the subdural space will hold should be injected through these tubes at three-hourly intervals, for the larger the quantity of fluid the more likely it is to spread to all parts of the subdural space and thus to prevent loculation. Withdrawal of ventricular or lumbar cerebrospinal fluid may enable larger amounts to be instilled into the subdural space. Within certain limits the concentration of the solution is probably less important than the bulk ; at present we recommend 500 units per c.cm., but further work is required to establish the optimal concentration.

In the early stages of the disease the subdural pus is not circumscribed, though it is not found in all parts of the subdural space, and the aim should be to flood the whole space with penicillin solution. It might be a good thing to pass a catheter on the healthy as well as on the affected side, when the disease is unilateral, though we have not yet done this. Likewise in the acute stage before loculation we have never passed a catheter over the medial surface of the hemisphere, which is the favourite place for loculation of pus. Probably a catheter for subdural penicillin alongside the posterior half of the falx at a fairly early stage of the illness would diminish the frequency of loculated subdural abscess, but this also we have not yet done before the pus has become loculated.

Subdural Abscess.—When subdural abscess is suspected it should be sought for by passing a brain needle through one or more burr-holes. The favourite site for abscess, alongside the posterior part of the falx or on the surface of the adjacent tentorium, can best be explored through a series of parasagittal parietal burr-holes, the needle being directed downwards and medially through the parietal lobe—a trans-cerebral exploration of the subdural space. When the abscess is found it should be aspirated, and replaced by a large dose of penicillin (100,000 units in 2 c.cm. saline) and 2 c.cm. of thorotrast. Radiographs should then be taken, especially tangential projections, to determine the situation and extent of the abscess. On subsequent days we have treated the abscess by daily intermittent aspiration (Case 3) or, preferably, by continuous drainage through an in-dwelling catheter (Case 4), and daily instillation of penicillin for at least five days. The in-dwelling catheter is usually best inserted between the falx and medial border of the posterior part of the cerebral hemisphere through a dural incision in the angle between the posterior end of the sagittal sinus and the adjacent lateral sinus of the appropriate side. Our limited experience suggests that when the infection has spread from the mastoid process the loculated subdural abscess may be difficult to treat. In such cases it might be better to insert one catheter beneath the lateral edge of the hemisphere, but it

is probable that the parasagittal catheter will also be required. Great rise of intracranial pressure may hinder insertion of this catheter, in which case a brain needle may be left in the abscess cavity for twenty-four hours, as in Case 3.

General Management.—The severity of illness in these patients may be extreme for three to four weeks. Stupor may interfere with swallowing so that the risk of aspirating fluids into the trachea and bronchi is considerable. Moreover, as Williams (1944) has pointed out, some of these patients with pansinusitis may have some pre-existing lung infection, and one of our patients developed an interlobar empyema or lung abscess (anærobic streptococcus) at the same time as purulent pachymeningitis. There must be the utmost care in administering fluids and for several days feeding should usually be by in-dwelling stomach tube. If respiratory symptoms arise the patient should be nursed with his head low, by raising the foot of the bed on blocks, even though his intracranial pressure is already raised. Blood transfusions are valuable in the acute stage of the infection. As fits are not infrequent, both in the acute stage and subsequently, phenobarbitone should be given for some months. Careful day-to-day clinical assessment and frequent examination of the pressure and cellular content of the lumbar cerebrospinal fluid are required in order to detect the onset of subdural loculation and other complications.

Operations.—The operative procedures are not usually extensive, a point of considerable importance in patients who are so very ill; but, as Table VIII shows, each patient had several operative sessions—as many as seven in one case. Burr-holes are required for detection of pus and insertion of penicillin tubes, or for ventriculography; bone may have to be removed for osteomyelitis of the skull or drainage of extradural abscess. In some cases operations on the paranasal sinuses or mastoid may be required, or purulent clots may need to be removed from the venous sinuses. Carotid arteriography may furnish useful information.

Until the technique of handling these subdural infections is further improved it seems to us that the best way of obtaining recovery is by frequent minor operative procedures designed to discover foci of pus and to apply penicillin to the subdural space and to any subdural abscesses which may have formed.

If a cerebral abscess develops it should be treated by excision through an osteoplastic flap when the residual subdural infection can also be dealt with Case 6).

Subarachnoid and Ventricular Penicillin.—The leptomeningitis varies in its severity, and subarachnoid or ventricular penicillin is not required unless the cerebrospinal fluid indicates a frank bacterial infection. However, when the medial and inferior parts of the subdural space are being explored for abscess across the cerebral hemisphere, or when the subdural space over the convexity is being explored through a field contaminated by the presence of osteomyelitis or extradural abscess, there must be a risk of setting up leptomeningitis or ventriculitis. This can be overcome by a single prophylactic injection of penicillin into the ventricle. For all purposes a dose of 10,000 to 15,000 units will give an adequate concentration of penicillin in the cerebrospinal fluid for twenty to twenty-four hours; large doses are not only unnecessary, they may also be harmful (Smith and others, 1946).

Osteomyelitis.—Spreading osteomyelitis of the skull is present in the majority of cases and is sometimes inconspicuous, particularly when penicillin has been given early in the illness. If not obvious it should be repeatedly looked for by radiographs during the course of the illness. With systemic penicillin maintained for eight to twelve weeks it seems likely that in most cases there will be no need to remove large areas of skull. The osteomyelitis will either subside without operation, as in Case 3, or with limited removal of pus and sequestra, as in Case 2. With penicillin it should rarely be necessary to undertake a massive removal of bone in the acute stage, as used to be done (Plate VI a). However, if after the subdural infection has been overcome any focus of sequestration and suppuration remains in the skull it should be removed, for such foci may harbour living bacteria for long periods and are apt to produce recrudescence of cranial or intracranial infection once penicillin is stopped. In cases treated with penicillin the radiographs may show areas of rarefaction which suggest foci of pus in the bone where none exist (Fig. 4).

Residual Infection.—Three of our ten cases (Cases 6, 7, and one other) developed further intracranial infection at a time when they appeared to have made a satisfactory recovery. Two had a cerebral abscess and the third probably had a medial loculated subdural abscess. In each case the symptoms were probably kept in check for a time by systemic penicillin, for they only appeared after the drug had been withdrawn. While in one of these cases the symptoms cleared up completely and permanently with a further and prolonged course of penicillin systemically, in the other two cases the subdural abscess was only "suppressed" by the penicillin and the patient subsequently developed a cerebral abscess. In view of the frequency of residual

infection we consider that the right course in all patients who have made a clinical recovery from pachymeningitis is to ensure, as far as is possible by means of ventriculography before the patient leaves hospital, that no focus of intracranial infection remains. If the ventricles are perfectly symmetrical it is reasonably certain that no abscess remains. We would stress again the advisability of keeping the patient under close observation for some weeks after penicillin has been stopped.

The Primary Focus.—In some cases it will be necessary for the otologist to deal radically with the primary infection in the paranasal sinuses or petrous bone. If possible, this operative treatment should be deferred for some months after the pachymeningitis, and systemic penicillin should be administered for some days before the operation.

Prophylaxis.—It seems likely that the incidence of purulent pachymeningitis, uncommon though it may be, could be considerably reduced with adequate prophylaxis. According to Turner and Reynolds (1931, p. 256) the condition arises most commonly in cases of chronic, or acute superimposed on chronic pansinusitis or mastoiditis, after some operative interference, sometimes no more than simple puncture of the maxillary sinus. As McKenzie (1913) said, "What seems to be an irreproachable operation is followed by progressive osteomyelitis," and one otologist described it as "like setting fire to shavings." In view of the proved efficacy of penicillin in the treatment of both the osteomyelitis and the purulent pachymeningitis there can be little doubt that these complications of sinus and mastoid surgery could be prevented by adequate doses of systemic penicillin for a few days before and after surgical intervention.

Summary

1. In the last twenty years we have had thirty-three cases of spreading purulent pachymeningitis. Of these, twenty-two followed pansinusitis, seven followed mastoiditis, and four were secondary to distant foci of infection. Spreading osteomyelitis of the skull, with or without osteomyelitis of the facial bones, was associated with purulent pachymeningitis in at least twenty-six cases; its presence is apt to be overlooked. Other associated lesions were: extradural abscess in sixteen cases; cerebral abscess in nine cases; severe leptomeningitis in seven cases, the remainder showing only a mild leptomeningeal reaction; thrombosis of the dural venous sinuses and/or the cerebral veins, sometimes purulent, in seven cases; abscess of the lungs in two cases; and in one case obstruction of the common carotid artery in the neck, discovered by accident during cerebral angiography, and probably due to thrombosis.

2. Of twenty-seven cases in which the bacteriology is recorded the subdural infection was due to streptococci in twenty-five cases (combined in one case with *Staphylococcus aureus*), to *Staphylococcus aureus* alone in one case, and to pneumococcus in one case in which there was also intense purulent leptomeningitis. The streptococci were grown in seventeen cases and were anærobic in ten, α-hæmolytic in six, and β-hæmolytic in one. In our experience *Staphylococcus aureus* produces osteomyelitis of the skull as frequently as the non-β-hæmolytic groups of streptococci, but rarely spreads diffusely through the skull or produces purulent pachymeningitis as the non-β-hæmolytic streptococci do, though it frequently produces brain abscess. These differences of behaviour of the two groups of bacteria are not explained.

3. In one case the causal anærobic streptococcus was not inhibited *in vitro* by 5 units per c.cm. of penicillin. In three other cases the streptococcus was completely inhibited by 0·04 units per c.cm. of penicillin or less. In all ten cases which were fully treated with penicillin (non-β-hæmolytic streptococci eight, *Staphylococcus aureus* one, and pneumococcus one) the clinical response indicated that the infecting organism was sensitive to penicillin.

4. The clinical picture of purulent pachymeningitis is characteristic and corresponds to a diffuse paralysis of the cortex of one cerebral hemisphere associated with rise of intracranial pressure.

5. Before the introduction of penicillin eighteen patients were treated by removal of variable amounts of osteomyelitic skull and attempts to drain the subdural space; all died. When limited amounts of penicillin became available five patients were treated by local instillation of penicillin into the subdural space and all of these died.

6. Ten cases have been fully treated with penicillin by systemic, subdural, intraventricular, and subarachnoid routes. Of these seven recovered. In six of these patients the late result is known from six months to four years after recovery from acute symptoms; in all except one, who had a cerebral abscess as well, the functional recovery is complete or almost complete, but four of the patients have infrequent fits.

7. Penicillin passes freely from the blood stream to the subdural space. In spite of this we found it necessary to instil penicillin solution directly into the subdural space. The details of this method are described.

8. In seven of our ten fully-treated cases, after the diffusely spreading phase of the subdural space suppuration was overcome, the patient developed a loculated subdural abscess, and at a later stage in two of these cases there was abscess of the brain. The day-to-day assessment of these cases, and the early recognition and operative treatment of the complications (and of the associated lesions) are far from easy; these aspects are discussed in detail.

9. Purulent pachymeningitis most commonly follows operation for chronic pansinusitis or mastoiditis, and its incidence should be considerably reduced by maintaining an adequate concentration of penicillin in the blood before, during, and after these operations.

References

Cairns, H. (1930). *Proc. roy. Soc. Med.*, **23,** (Sect. Otol.), 49.

——(1937). *J. Laryng.*, **52,** 589.

——(1947). *Brain*, **70,** 251.

——, Calvert, C. A., Daniel, P., Northcroft, G. B. (1947). *Brit. J. Surg.* War Surgery Supplement No. 1, p. 198.

——, and Russell, D. S. (1946). *J. Path. Bact.*, **58,** 649.

Dreyfuss, R. (1896). "Die Krankheiten des Gehirns und seiner Adnexe im Gefolge von Naseneiterungen." Jena.

Gilmour, J. R. (1941). *J. Path. Bact.*, **53,** 263.

Hempstead, B. E. (1944). *Proc. Mayo Clin.*, **19,** 480.

Kubik, C. S., and Adams, R. D. (1943). *Brain*, **66,** 18.

Kuhnt, H. (1895). "Ueber die entzündlichen Erkrankungen der Stirnhöhlen und ihre Folgezustände." Wiesbaden.

McKenzie, D. (1913). *J. Laryng.*, **28,** 6.

Moniz, E. (1941). "Trombosis y otras Obstrucciones de las Carotidas." Salvat. Editores, S.A. Barcelona.

Penfield, W. G. (1924). *Anat. Rec.*, **28,** 173.

Robertson, W. F. (1900). "A Textbook of Pathology in Relation to Mental Diseases." Edinburgh. Clay. p. 285.

Sandusky, W. R., Pulaski, E. J., Johnson, B. A., Meleney, F. L. (1942). *Surg. Gynec. Obstet.* **75,** 145.

Sherman, J. M. (1937). *Bact. Rev.*, **1,** 3.

Smith, H. V., Duthie, E. S., and Cairns, H. (1946). *Lancet*, **1,** 185.

Turner, A. L., and Reynolds, F. E. (1931). "Intracranial Pyogenic Diseases." Edinburgh. Oliver and Boyd.

Tutton, G. K., and Shepherd, W. H. T. (1948). In the press.

Weed, L. H. (1932). In "Cytology, and Cellular Pathology of the Nervous System." Edited by Wilder Penfield. Vol. 2, p. 611.

Williams, H. L. (1944). *Proc. Mayo Clin.*, Hoeber. New York. **19,** 474.

Williams, H. L., and Heilman, F. R. (1937). *Arch. Otolaryng., Chicago*, **25,** 196.

NECROSIS OF THE BRAIN DUE TO RADIATION THERAPY

CLINICAL AND PATHOLOGICAL OBSERVATIONS

BY

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In treating intracranial tumours with deep *x* rays or radium the aim is to direct the largest possible dose of radiation to the tumour within the limits of safety for the normal tissues. Even with the standard dosages in current use, irradiated areas of the scalp suffer temporary or permanent epilation. Excessive radiation is known to cause burns and necrosis of the scalp and skull, and harmful effects on the underlying brain. These complications are usually manifest within a short time of treatment and they may be largely avoided by using multiple portals of entry so that no one area of the overlying or surrounding tissues receives more than a fraction of the total dose brought to bear on the tumour. In fact the technique of therapy is so well developed that serious damage to normal structures is regarded as a rare occurrence.

Nevertheless we have encountered in recent years a series of cases in which harmful effects to the brain have followed standard dosages and technique without serious superficial damage, and at long intervals after the termination of treatment. Although the effects were not strictly uniform in every case, the similarity was close enough in each, and so different from other pathological processes, that it seems reasonable to relate them to the single common feature of radiation treatment. In brief, the lesion was an extensive subcortical necrosis, maximal in the field which received the most radiation. In some cases the clinical effects came on after a long latent interval with the suddenness of a vascular accident; in others they were slowly progressive, clinically suggesting a recurrence of the tumour for which the radiation treatment had been given. In the fatal cases the lesion seemed to be largely responsible for death.

Nine cases have been examined. Eight of these had had various surgical procedures for cerebral neoplasms followed by one or more courses of radiation treatment. The other case is of particular interest because so far as can be known the brain was normal before radiation treatment was instituted for a rodent ulcer of the scalp. This case will be described first, followed by four others which are representative of the remainder.

Case Reports

CASE 1

Rodent ulcer of scalp. Multiple excisions followed by x radiation. Nine months later epilepsy and hemiplegia. Radium treatment of ulcer in preparation for craniotomy. Aggravation of cerebral symptoms. Operation: excision of necrotic lesion of left temporal lobe. Recovery. (R.I. 21380/44.)

A man aged 52 years was admitted to the Radcliffe Infirmary, Oxford, on Jan. 14, 1944, suffering from aphasia and epileptic attacks. At the age of 37 a warty growth was excised from the left parietal region of the scalp, above and behind the left ear. It was found to be a rodent ulcer, and recurrences were excised on several occasions, the last being in March, 1943. Immediately afterwards he was given deep *x*-ray treatment to the affected area (a single exposure of 2,300 r. The physical factors were: kV. 230; milliamps. 10; ½ H.V.L. 1·3 mm. of copper; F-s distance 29 cm.; size of field circle 7 cm. diameter; time of exposure 10 minutes 12 seconds).

The scalp never quite healed, and in the three or four months before his admission to the Radcliffe Infirmary a further recurrence was obvious.

Apart from a little local discomfort at the site of the growth and the inconvenience attendant on its size and position, he had no symptoms until Dec. 19, 1943, when his speech suddenly became confused, and within a few moments his right arm began to jerk convulsively and he lost consciousness for several minutes. When he recovered, he seemed dazed and was unable to express himself in speech or writing. There was no obvious paralysis of his limbs. Another attack occurred about three hours later, and in this one he was unconscious for nearly an hour, with what was described as generalized convulsions. He was then taken to a hospital where shortly after admission he had a third attack. When he recovered consciousness he had considerable aphasia,

but no other neurological abnormalities were detected. There was no headache or vomiting. The spinal fluid pressure was increased but the fluid was normal on analysis. It was thought that the aphasia and the epileptic attacks were due to invasion of the meninges and brain by the rodent ulcer, and arrangements were made for the patient's transfer to the Radcliffe Infirmary.

On admission he was a healthy looking man, somewhat distressed by considerable aphasia affecting all aspects of the language function. He had no recollection of the epileptic attacks or of any events for the four days following them. There was a rodent ulcer, 4 cm. in diameter, in the left lower parietal region with a thick yellow crust in its centre. The scalp for 1 cm. around the periphery of the ulcer was thin, shiny, and adherent to the underlying skull. The neurological examination revealed normal optic fundi, full visual fields, normal pupils and ocular movements, and slight weakness of the right side of the face and right upper limb. The tendon reflexes were slightly increased in the right upper limb, but the other reflexes were normal. There was no sensory disturbance. The spinal fluid pressure was normal (140 mm.) but the fluid contained 80 mg. of protein per 100 c.cm. and 4 lymphocytes per c.mm. Radiographs of the skull were normal: there was no abnormality in relation to the rodent ulcer, and the pineal shadow was situated in the middle line. The general examination was negative. The blood pressure was 130/90 mm. Hg.

The possibility of a radiation effect was considered, but it was thought that the dosage was too small and that a neoplasm or abscess related to the superficial tumour was more likely. In view of the possible need to reflect an osteoplastic flap in the vicinity of the ulcer, an attempt was made to heal the ulcer by the insertion of 40 mg. of radium needles on Jan. 25, 1944, and these were left in situ for 120 hours.

Within two days of the insertion of the radium, the patient began to deteriorate. He complained of a little headache, he was observed to be sleeping more than normally, and the aphasia and right hemiparesis became more pronounced. He seemed to resent painful stimuli less on the right side of the body than on the left, though the aphasia made it difficult to assess sensory abnormalities. There seemed to be no hemianopia. On Feb. 6, the spinal fluid pressure was 200 mm., and the fluid now contained 180 mg. of protein per 100 c.cm. and 9 lymphocytes per c.mm. Radiographs of the skull taken on Feb. 10 showed that the pineal shadow was now displaced to the right side of the middle line.

Operation.—The evidence for a progressive lesion in the left cerebral hemisphere was thus clear and the possibilities of abscess or neoplasm had yet to be excluded. An arteriogram (thorotrast) was done, but the findings were not definite, so a ventriculogram was done on Feb. 10. Only the right ventricle could be found and filled with air: it was markedly displaced to the right side. In seeking the left ventricle the brain cannula met a tough resistance in the temporo-parietal region. An osteoplastic flap was reflected in the left temporo-parietal region, with the scalp ulcer—much cleaner and smaller since the application of radium—in the centre of its base. The scalp was lightly adherent to the pericranium in the vicinity of the ulcer, but it separated easily with blunt dissection. The pericranium itself, the skull, and the dura appeared normal. When the dura was opened a lesion was clearly apparent in the posterior part of the temporal lobe, exactly underneath the rodent ulcer. In a sharply circumscribed area, 4 cm. from before back by 3 cm. from above down, the convolutions were broad, flat, and swollen and had a rather greasy, brownish appearance. They were very firm, almost hard to the touch. The surface blood vessels were not remarkable, but there was an excess of small visible vessels coursing over the convolutions. The surrounding brain appeared to be quite normal. A fragment of tissue was taken for rapid examination and its toughness was such that it had to be cut with a sharp knife. The provisional diagnosis at this stage was thought to be metastatic carcinoma and the mass was dissected out. The lesion looked fairly discrete but there were numerous white fibrous strands extending from the main mass out into the surrounding white matter, and these were so tough that they had to be cut with scissors. The deep surface of the mass abutted on to the wall of the ventricle in the posterior part of the temporal lobe.

Subsequent Course.—Convalescence was uneventful. The aphasia was much more marked for a few days after operation, but by the time he was discharged on Feb. 28 it was of about the same order as on admission. There was a complete right homonymous hemianopia. Eight months after operation the aphasia was much less marked, but even so prevented him from resuming work as a clerk. The hemianopia was complete in the upper quadrant, incomplete in the lower. There were no other neurological abnormalities. He had one epileptic attack, very much like the pre-operative ones, two months after operation, and another minor one about six months later. There were no more up to the time of the last follow-up in November, 1947, forty-five months after operation. By this time the hemianopia had receded to a sharp upper-quadrant defect, and the aphasia had diminished to the point where it was barely detectable in ordinary conversation. He was able to resume his work as a filing clerk in June, 1947.

Pathological Observations on the Specimen Removed at Operation

Macroscopic.—The leptomeninges were not obviously altered, but the blood vessels were engorged. The cortex on section was broadened in many places and, over the summits of the convolutions, was tough, grey, and indistinctly demarcated from the white matter. The latter was firm, unusually opaque and creamy-white throughout the specimen. It contained numerous petechial hæmorrhages, especially just beneath the cortex (Fig. 1).

Microscopic.—The leptomeninges had undergone slight fibrous thickening and were diffusely infiltrated with a few polymorphonuclear leucocytes and lymphocytes. A little recent hæmorrhage was present in places, probably the result of operative manipulation. There was slight fibrous thickening of the adventitia of a few of the larger arteries and veins. The cortex was altered

everywhere by changes which reached their greatest intensity over the summits of the convolutions. Thus there was a progressive loss of neurones, becoming almost complete at the summits, accompanied by gliosis that was in general dense, but less cellular over the convexities of the convolutions (Fig. 2). Surviving neurones showed dropsical swelling of the cell-body with stages of chromatolysis. In many the outlines of the cells were greatly crenated. The nuclei were frequently pyknotic. Some neurones were shrunken and hyperchromatic. The astrocytes were conspicuous for their large size and wealth of processes (Fig. 3). In certain areas they showed clasmatodendrosis with the formation of "amœboid glia." In these foci the perforating blood vessels had undergone thrombosis, and the surrounding tissue was necrotic and contained extravasated red corpuscles. Gliosis beneath the pia had resulted in a remarkable brush-like formation of the fibres (Fig. 3). In the areas of greatest destruction of neurones there was a pronounced lack both of oligodendroglia and microglia. Surviving oligodendroglial cells were hypertrophied and had well-preserved, unusually long processes. The microglial cells were in active amœboid phases and were found mostly in foci of actual necrosis and hæmorrhage. In the better preserved parts of the cortex, that is, in the depths of the sulci, many reacting microglial cells were present; the oligodendroglial cells were still somewhat scanty and many were in advanced stages of acute swelling.

The perforating vessels were extensively altered by fibrinoid necrosis and were often thrombosed. Many were greatly engorged. Thrombosis was often accompanied by recent perivascular hæmorrhages. Almost the entire cortex was unevenly permeated by interlacing filaments of fibrin. There was no histological evidence of antecedent hæmorrhages; in particular no iron pigment was found. In some of the cortical vessels there was great fibrous thickening of the adventitial sheaths and focal infiltration with thin cuffs of lymphocytes. Particles of thorotrast were often present in the walls of the vessels, especially in the adventitial cells.

Massive necrosis involved all parts of the *white matter*. It was permeated with densely matted fibrin filaments, and was unevenly infiltrated with considerable numbers of degenerating and fragmented leucocytes (Fig. 4). Many hæmorrhages were present, often surrounding vessels that had undergone fibrinoid necrosis and thrombosis. Other vessels showed conspicuous collagenous thickening, mostly involving the adventitial sheaths (Fig. 5) and some, in silver preparations, bore brush-like tufts of reticulin fibres that extend from the adventitia in to the adjacent tissues (Fig. 6). All normal cellular components of the white matter had disappeared except the microglial cells. These were in amœboid phases, contained sudanophil material, and were unevenly distributed. For the most part they occupied zones about the necrosis, particularly at the junction of grey and white matter. Extracellular particles of sudanophil lipoid were scattered through the necrotic white matter.

Small fragments of the *left temporal bone* removed at operation were microscopically of normal texture but showed loss of bone cells from many areas. The loss was patchy and nowhere amounted to frank necrosis of the bone. Osteoblasts were absent from the margins of the trabeculæ. Apart from an occasional granular myelocyte and a few plasma cells there was complete absence of hæmogenetic tissue from the medullary spaces. These were occupied by spongy connective tissue containing few spindle cells and occasional foam cells. In places a lightly eosinophil coagulum containing filaments of fibrin filled the interstices. The blood vessels were engorged and dilated. Fibrinoid swelling and degeneration was present in the wall of one arteriole, and a second was occluded by thrombus. In some of the medullary spaces the tissue showed degeneration and partial necrosis with pyknosis of the nuclei.

COMMENT.—Of particular interest in this case is the exacerbation of the neurological disturbance which occurred after the insertion of radium. The focal abnormalities became more marked and symptoms and signs of increased intracranial pressure appeared. The pineal gland was displaced and there was an increase in the protein and cellular content of the spinal fluid. There can be little doubt that these changes were initiated by the *x*-ray treatment, and greatly accelerated by the radium.

It is also of interest that so much improvement occurred at such a long interval after the acute manifestations. This is of importance, because in other cases the changes have been steadily progressive. We have recently observed an almost identical case, not included in this series, in which radiation of a rodent ulcer in the right parietal region was followed after several months by rapidly progressive left hemiplegia and hemianopia, with headache and papillœdema. At an exploratory operation a very similar lesion to that described above was found, and representative portions were taken for histological examination. They showed the same changes as in Case 1. The headache was temporarily relieved by the decompression and the papillœdema resolved, but three months later there was a large, tense cerebral hernia and the patient again began to suffer from headache. He gradually became stuporous and died in coma five months after operation. In this case the changes set in train by the radiation were clearly progressive, were not arrested by operative intervention, and were directly responsible for death.

CASE 2

Colloid cyst of third ventricle mistaken for glioma extending into left temporal lobe. Subtemporal decompression. X-radiation therapy. Death later from hydrocephalus. Multiple areas of necrosis and softening of brain. (R.I. 16246/43.)

A woman aged 53 years was admitted to the Radcliffe Infirmary, Oxford, on March 13, 1940. She had been in good health until a year before admission, when she

began to have frequent paroxysmal headaches. In June, 1939, these headaches ceased and did not recur. At this time, however, she began to have peculiar attacks of transient loss of contact with her surroundings: she described such an attack as beginning with a peculiar feeling in the abdomen which surged up over her head, and then she would become "confused" for a few moments. If anyone spoke to her she would not be able to understand, nor could she reply. At times during attacks when she was alone she seemed to hear a voice speaking to her but could never remember what was said. At times too she had a feeling that she was in a different place from that in which she actually was, but the details were not clear enough for identification or recollection. There were no olfactory or gustatory components. Witnesses observed many such attacks and reported that she "went pale and vacant" for a few moments, but there were no convulsive movements and no incontinence. She recovered promptly, and resumed what she had been doing before the attack. There was no headache nor pain of any kind associated with these episodes. In December, 1939, she lost consciousness in two of the attacks, on each occasion for about half an hour. There were no convulsive movements, and no sequels. She admitted to no other symptoms, and she came into hospital for investigation of the attacks which were occurring four or five times a day.

On examination the patient was seen to be a healthy-looking middle-aged woman. Her face was somewhat hirsute, and she said that, although it had always tended that way, the growth of hair had been more pronounced in the six months before admission. She gave a good account of herself, and there was no obvious mental impairment. She was right-handed, and there was no aphasia. The general physical examination revealed no significant abnormality. Her blood pressure was 130/80 mm. Hg. Examination of the nervous system disclosed the following abnormalities. Both optic discs were a little blurred but there was no measurable swelling, the appearances being interpreted as being due to a pre-existing papillœdema which had resolved. Visual acuity was normal, but there was an incomplete right homonymous hemianopia. There was a very slight weakness of the right side of the face and of the right limbs, but the reflexes were all normal and there was no sensory disturbance.

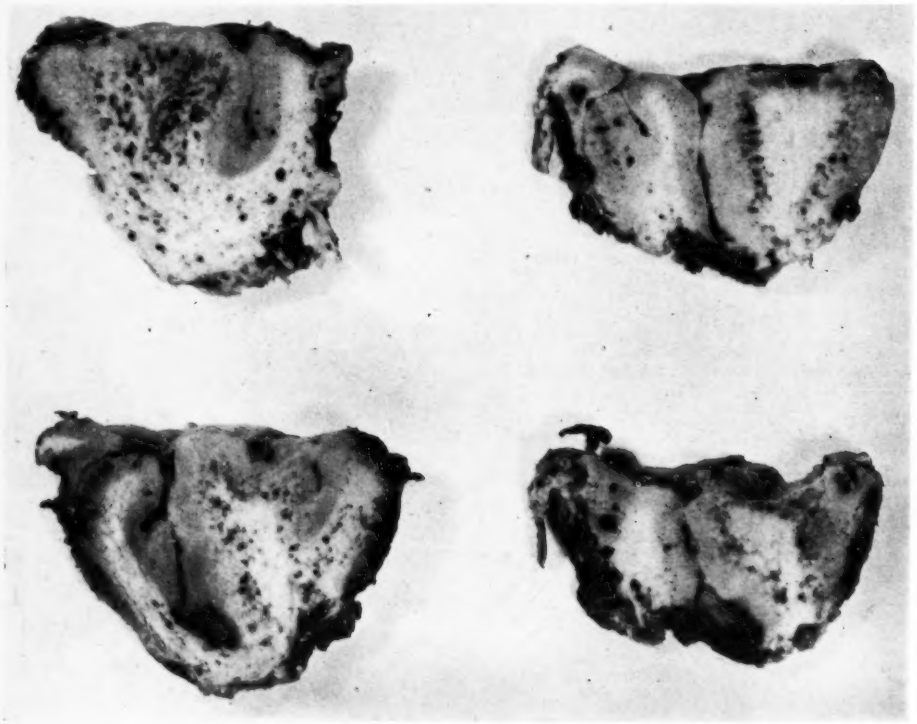
The cerebrospinal fluid pressure was 160 mm., and the fluid contained 60 mg. of protein per 100 c.cm. In other respects it was normal. Radiographs of the skull were normal.

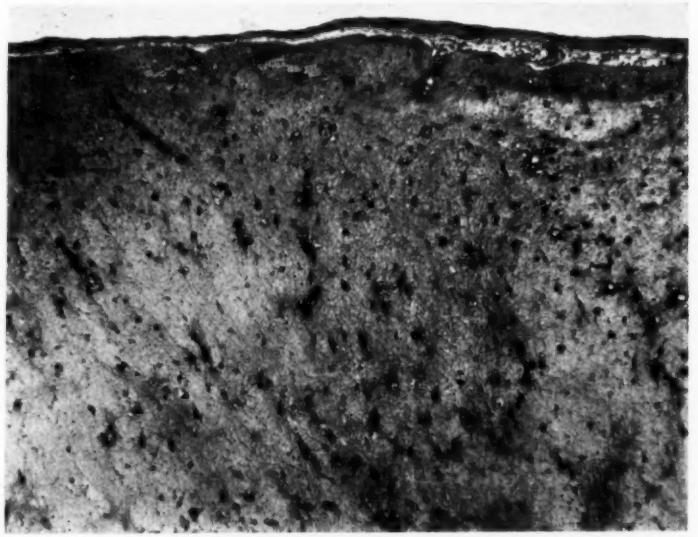
From the character of the attacks, the right-sided hemianopia, and the slight right hemiparesis, it was thought that she had a lesion, probably an infiltrating tumour, in the depths of the left hemisphere, but the evidence for location and nature of the lesion was clearly too slight to dispense with a ventriculogram. This revealed a slight symmetrical dilation of the lateral ventricles without lateral displacement. There was a constant filling defect in the roof of the third ventricle, posterior to the foramina of Monro. The appearances were interpreted as being due to a neoplasm in this situation, but to explain the hemianopia and the right hemiparesis it was thought that there must be a lateral extension into the left cerebral hemisphere and that an infiltrating glioma was most probable. On March 19, 1940, a right temporal decompression was done, as it was considered that the ventricles were too little dilated to make a transventricular exploration of the lesion practicable. She stood the operation well and convalescence was uneventful.

She was given her first course of deep *x*-ray treatment between April 22 and June 17, 1940. (The physical factors were: field size, 8·6 cm. diameter; kV. 190; milliamps 6; distance 70 cm.; filter 1 mm. copper; thirty treatments at 300 r (180 r), three treatments at 200 r (72 r), through right and left lateral and vertical portals; total tumour dose 3,492 r.)

She continued to have attacks of the same nature as before her treatment, but in other respects she was well and leading a normal life. When she reported on June 19, 1941, fifteen months after operation, the decompression area was indrawn and there were no neurological abnormalities except the right hemianopia, which was unaltered. She had two further courses of deep *x*-ray treatment through right and left lateral portals only: (1) from Nov. 19, 1940, to Dec. 31, 1940, nineteen treatments at 200 r (72 r), and four treatments at 300 r (108 r), the total tumour dose being 1,800 r; (2) from March 12, 1942, to April 10, 1942, twenty treatments at 200 r (72 r), the total tumour dose being 1,440 r. The physical factors were the same as in the first course. At the end of 1942 the attacks suddenly ceased, and she was entirely free from symptoms until the end of June, 1943, when she began to complain of loss of energy. Early in July it was noticed that her memory was failing and she began to lose interest in her family, her home, and her personal appearance. At the end of July it was noticed that her gait had become slow and laboured and she was dragging her left leg. By the first week in August she was unable to get up. Her speech became slow, monotonous, and thick, and she seemed to have difficulty in swallowing. She was incontinent of urine and fæces. During the first week of September she ceased speaking altogether although she was not unconscious. She had never complained of headache or any pain.

She was readmitted to hospital on Sept. 24, 1943. Although quite conscious, she was mute and was never heard to utter a sound. She could swallow liquids and semi-solids, but slowly, and would keep food in her mouth for hours if not prompted to swallow it. She was immobile in bed and made no attempt to change her position. She was incontinent of urine and fæces. The decompression area was tense and bulging (her husband said it had been so for about two months before admission) and there was considerable swelling of both optic discs, with hæmorrhages and exudate in the fundi. Her co-operation could not be obtained for assessment of visual acuity or fields, but she seemed to be able to see and the pupils reacted briskly to light. There was profound paralysis of conjugate movement of the eyeballs: movement to the left, upwards, and downwards was lost, although she could look to the right side. There was complete left hemiplegia affecting the face,





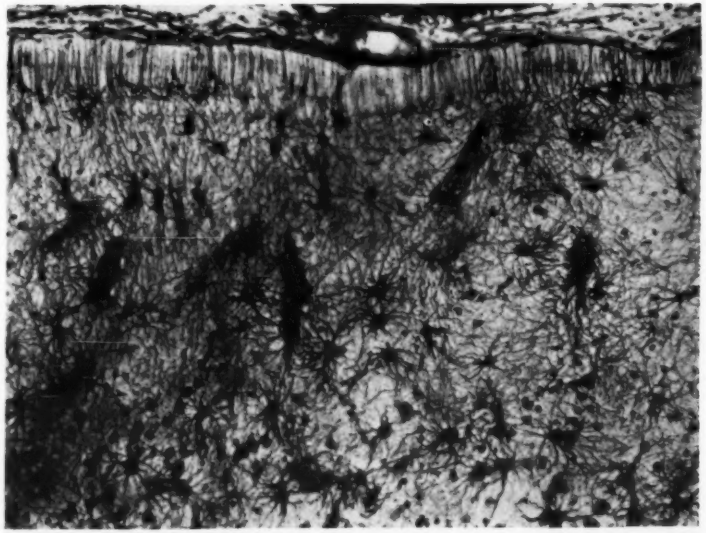


FIG. 1 (above).—Case 1. Sections of mass removed at operation. Note broad pale cortex and numerous hæmorrhages in subcortical white matter.

FIG. 2 (top right).—Case 1. Summit of convolution showing loss of neurones. Hæmatoxylin and eosin, ×89.

FIG. 3 (lower right).—Case 1. Same area as in Fig. 2, showing gliosis and brush-fibres in sub-pial zone. Silver carbonate, ×92.

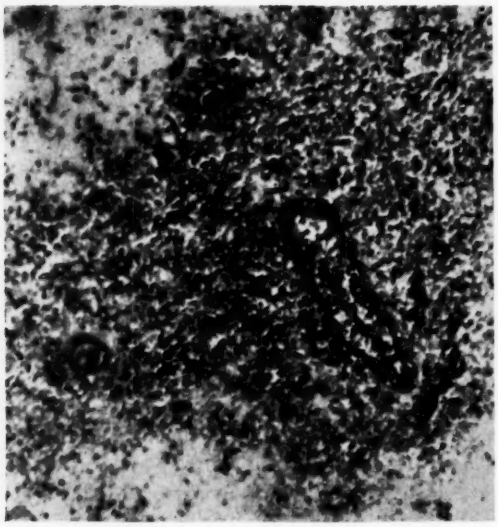


FIG. 4 (top left).—Case 1. Fibrinoid necrosis of vessel in white matter surrounded by degenerating leucocytes. Hæmatoxylin and eosin, ×160.

FIG. 5 (above).—Case 1. Collagenous thickening of blood vessel in necrotic white matter. Silver carbonate, ×150.

FIG. 6 (lower left).—Tufts of reticulin fibres extending from vessels into necrotic white matter. Silver carbonate, ×108.

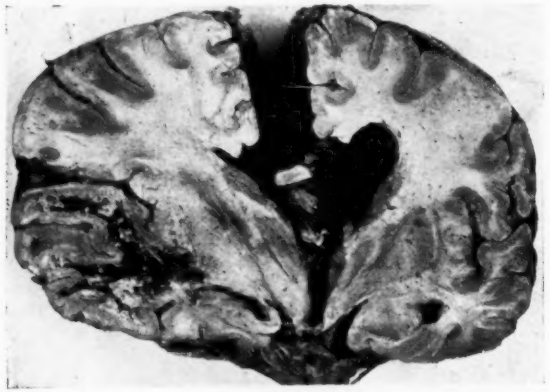


FIG. 7 (above).—Case 2. Small colloid cyst in third ventricle and massive subcortical necrosis of right temporal lobe.

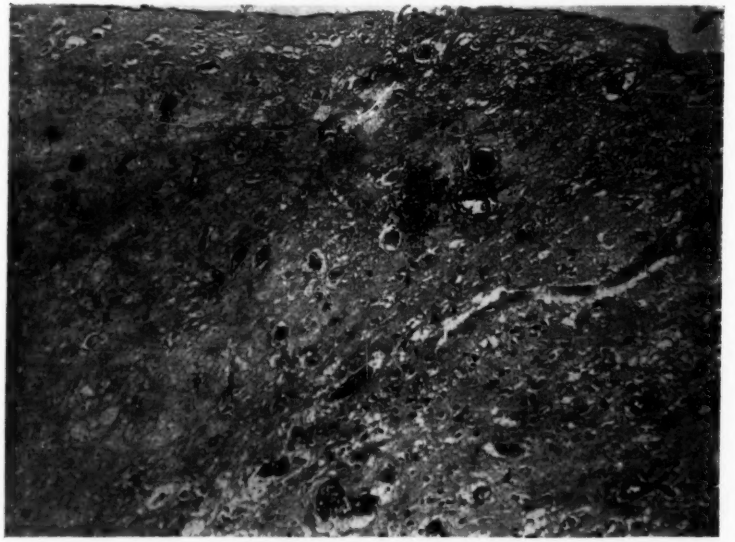


FIG. 8 (right).—Case 2. Necrosis of cortex at summit of temporal convolution, with small perivascular haemorrhages. Hæmatoxylin and eosin, ×89.

FIG. 9 (above).—Case 2. Collagenous thickening of vessel in white matter of right temporal lobe. Hæmatoxylin and van Gieson, ×200.

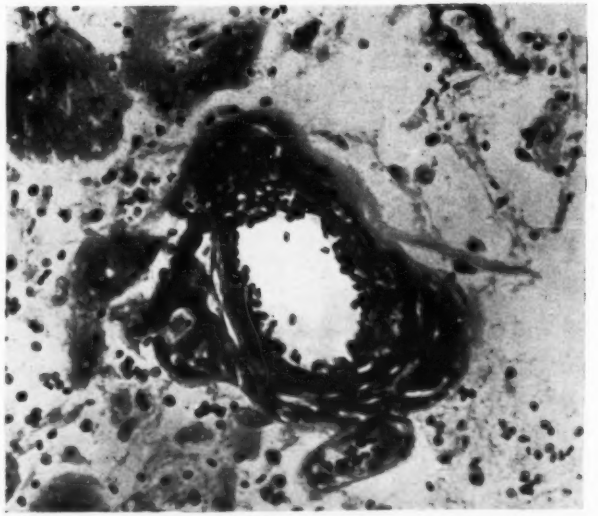


FIG. 10 (right).—Case 2. Fibrinoid necrosis of vessel in a cavity in white matter of right temporal lobe. Hæmatoxylin and van Gieson, ×250.

arm, and leg (it was not possible to learn how this had developed, but from the husband's account it was rapid rather than sudden, probably becoming complete between the middle of July and the end of August, 1943). The right limbs were somewhat spastic, and there was involuntary grasping in the right hand. All the tendon reflexes were exaggerated. Both plantar responses were extensor. She seemed to resent painful stimuli less on the left side of the body than on the right. The spinal fluid pressure was 330 mm. The fluid was slightly yellow and contained 80 mg. of protein per 100 c.cm.

These findings clearly indicated a lesion in the right cerebral hemisphere, whereas on the previous admission three and a half years earlier the evidence pointed to a left hemisphere lesion. The ventriculogram was repeated and this showed dilatation of the left ventricle, with displacement of it and the third ventricle to the left side. The right ventricle was incompletely outlined, but what air was in it suggested a large space-occupying lesion in the central part of the body of the ventricle extending into the thalamus. In searching for the right ventricle, the exploring needle had encountered a small cyst containing a few drops of yellow fluid, and some tough fibrous tissue was recovered from the lumen of the needle. This was spread on a glass slide and stained with toluidine blue. The appearance was that of a fibrillary astrocytoma, and the lesion was considered inoperable. She become more drowsy and died in coma on Oct. 7, 1943.

NECROPSY EXAMINATION.—At necropsy the brain showed great convolutional flattening. A small colloid cyst, measuring 0·7 by 0·6 cm., occupied the anterior part of the third ventricle, occluding the right foramen of Monro rather more than the left (Fig. 7). There was massive subcortical necrosis of the right temporal lobe beneath the site of the old decompression. This area measured 5·5 by 4·5 cm. in the coronal plane and 6·5 cm. from before back. In most areas the cortex appeared to be intact, though it frequently displayed an ill-defined zone of brownish discoloration along its deep border. Towards the anterior end of the decompression the superficial cortex appeared to be replaced by firm grey tissue. The white matter of the temporal lobe was, for the most part, sunken and brownish and contained many irregular cavities traversed by bands of yellowish necrotic tissue and grey thickened blood vessels. Between this and the cortex was a zone, up to 1 cm. deep, of friable opaque creamy-white necrosis. The necrosis extended into the lower border of the Island of Reil and to within 0·1 cm. of the temporal horn, which was considerably expanded.

There was considerable œdema of the white matter of the right frontal lobe, but the remainder of the cerebral hemispheres appeared normal. In particular there was no macroscopic abnormality in the left temporal region, nor in the tissue at the vertex. At the level of the anterior corpora quadrigemina the lumen of the aqueduct was deformed and displaced to the left, while an ill-defined grey opaque area occupied the site of the right oculomotor nucleus. A similar area, about 0·4 cm. in diameter, was identified in the right side of the tegmental portion of the pons just beneath the floor of the fourth ventricle.

MICROSCOPIC EXAMINATION

Right Temporal Lobe.—The right temporal lobe was involved in changes of the same range and character as those described in Case 1. The amount of total destruction of the tissue was, however, greater. Thus the summits of the convolutions at the site of the decompression were entirely devoid of cells, apart from a few subpial astrocytes in advanced stages of degeneration (Fig. 8). Even the perforating blood vessels were for the most part pale and structureless, but a few showed fibrinoid necrosis and retained some of their endothelial nuclei. In the depths of the sulci the necrosis and degeneration were progressively less intense. Swollen fibrillary astrocytes contributed to a gliosis that was less conspicuous than in Case 1, and was found mainly in the deeper laminæ of the cortex. The massive necrosis of the white matter was interrupted by considerable areas of recent hæmorrhage. Irregular cystic spaces often surrounded greatly thickened, hyaline blood vessels (Fig. 9). The presence of macrophages laden with iron pigment in the walls of some of these spaces suggested their origin from antecedent hæmorrhages.

There was great collagenous thickening of the larger meningeal arteries and veins in the sulci. A similar thickening affected the perforating vessels and was more conspicuous than in Case 1, while fibrinoid necrosis of these vessels was on the whole less prevalent, though spectacular when present (Fig. 10). Recanalization of an antecedent thrombus was found in a few perforating vessels.

The white matter in the posterior border of the area was interrupted by large, irregular, often anastomosing areas of necrosis always accompanied by fibrinoid necrosis, and often thrombosis, of the included vessels. There was much albuminous hyaline coagulum in the interstices of the adjacent tissue, many large foam cells, and areas in which gliosis is conspicuous. The astrocytes participating in this were greatly swollen and hypertrophied and had long, coarse processes. Many perivascular areas of hæmorrhage were present. A number of vessels, both here and in the more central parts of the necrosis, were cuffed with a mixture of lymphocytes, large mononuclear cells, and foam-cells.

Mid-Brain.—There was œdematous swelling of the right side extending throughout the tegmental region. The vessels were engorged and, in some of the larger meningeal arteries and veins there was recent—probably agonal—thrombosis. Recent perivascular hæmorrhages were present about a few perforating vessels, both dorsal to the right crus and in the grey matter adjacent to the right ventro-lateral border of the aqueduct. An area of anæmic necrosis lay to the right of, and parallel with, the median raphe. A few similar but smaller foci of necrosis, and of œdema without necrosis, occupied the right side of the pons in both basal and tegmental areas. The blood vessels again were engorged. A few minute pericapillary hæmorrhages were present in the tegmental region on the right.

Left Temporal Lobe.—The left temporal lobe was normal except for a small patch of recent softening in the medial border of the uncinate gyrus. The softening was

accompanied by a collection of amœboid microglial cells and local fragmentation of the axis-cylinders with the formation of retraction balls. There was no demonstrable gliosis.

There was no visible abnormality in the cortex and white matter of the left upper Rolandic region.

CLINICAL COMMENTARY.—It is difficult to relate the necropsy finding of a colloid cyst in the third ventricle to the symptoms for which the decompression and radiation treatment were given. The attacks were regarded as a kind of diencephalic epilepsy, and it is possible that these were due to the hydrocephalus resulting from foraminal obstruction by the colloid cyst, although we have not encountered this symptom in other cases of hydrocephalus due to a colloid cyst. No satisfactory explanation was found for the right hemianopia and the weakness of the right limbs. The irradiation necrosis was doubtless confined to the right temporal region because the bone had been sacrificed at this site, thus permitting the entry here of a greater proportion of the *x* rays than elsewhere. The changes in the brain stem were of a recent acute character. There was no gliosis. From their position and character it is less probable that they were related to the irradiation of the brain than to disorders of the vascular supply consequent upon increase in intracranial pressure above the tentorium. Equally, the fragmentation of axis cylinders in the white matter and focal softening of the adjacent cortex in the medial border of the left uncinate gyrus are attributable to pressure by the free edge of the tentorium. There was no alteration in the left temporal lobe over its lateral aspect where irradiation of this field might have been expected to produce changes.

COMMENT ON CASES 1 AND 2

The similarity of the pathological changes in these two cases is striking. In both there was a massive subcortical necrosis in the irradiated area apparently caused by reactions in the perforating vessels: collagenous thickening, fibrinoid necrosis, and thrombosis of these were all conspicuous features, and relatively few were unaltered. It is remarkable that the meningeal vessels, by contrast, had escaped all but the most trivial alterations. The cortex, though on the whole less affected than the white matter, had lost most if not all of the neurones from the summits of the convolutions without, however, undergoing the atrophy that might have been expected. This lack of shrinkage cannot be satisfactorily explained even if it is assumed that the loss of neurones was a gradual piecemeal process with a concomitant replacement gliosis. Such a gradual loss is seen in general paralysis and in old age; in both these conditions cortical atrophy is conspicuous. A further remarkable feature in both these cases was the widespread permeation of the tissue with fibrin. The presence of this change in Case 2 suggests that it was of a persistent character; it cannot at any rate be interpreted as an operation artefact. Such an escape of fibrin into the tissue must be attributed to an increase in the permeability of the perforating vessels, and this vascular change was said by Scholz and Hsu (1938) to occur in a few weeks after irradiation of the brain. Such an escape of fibrin may support and even expand the cortex and thus counteract the tendency to atrophy. The presence of granules of thorotrast in some of the adventitial cells of the perforating blood vessels in Case 1 is evidence of retarded circulation and increased vascular permeability.

Further peculiarities are to be noted in the glial reactions. Thus the astrocytes partaking in the gliosis were individually of a luxuriance seldom seen except in tumours of these cells. The microglial reaction was, however, disproportionately slight in relation to the degeneration and necrosis. The degree of neuronal degeneration present would ordinarily have been the signal for a conspicuous development of rod cells. But this reaction is in abeyance. It is true that a number of amœboid microglial cells were present but they were, for the most part, confined to areas of frank necrosis or to the borders of such areas. Their processes often presented a stunted appearance and a poverty of development that collectively suggest that these cells are in stages of degeneration as well as activation. The oligodendroglia was not conspicuously altered: in Case 1 there is acute swelling in many areas, while curious hypertrophic forms, not ordinarily seen except in tumours of these cells, were present in the cortex over the summits of convolutions.

In both cases there is histological evidence of a progression of the lesion, shown by the presence of fresh hæmorrhages, and fibrinoid necrosis with recent thrombosis of vessels. While in Case 1 such lesions might be explained by the pre-operative insertion of radium into the adjacent rodent ulcer of the scalp, in Case 2 there is no such clinical factor to explain an outcrop of fresh vascular lesions. There is, however, no means of estimating the age of the lesion or of relating it to the remarkable latent period that elapsed in both cases between the time of irradiation and the onset of symptoms. In Case 1 this latent period was nine months; in Case 2 it was at least sixteen months.

CASE 3

Right frontal spongioblastoma multiforme. Operation: partial removal and decompression. Three

courses of radiation therapy in the next twelve months. Freedom from symptoms in the next five years. Death seven years after operation. Extensive brain necrosis without recurrence of tumour.

L.W., a woman aged 22, came under observation on April 29, 1935, when she was admitted to the National Hospital, Queen Square, London, under the care of Dr. Macdonald Critchley. She had always been in good health until two months before admission, when she had a mild febrile illness regarded as influenza. This illness ran a short course, and after a fortnight she seemed to have recovered, but from about that time she began to complain of right frontal headache. Five weeks before admission she had an epileptic attack initiated by twitching of the left side of the face and the left upper limb. She was unconscious for about thirty minutes, in which time she bit her tongue and was incontinent of urine. When she recovered consciousness she had a very severe headache but there were no other remarkable sequels. From that time she was rarely free from headaches and vomited frequently. One week before admission she had another epileptic attack similar to the first one, and she subsequently noticed some weakness of the left hand.

On admission she was rather thin but did not look particularly ill. Although drowsy she could be roused to give a good account of herself and to co-operate in a full examination. The neurological abnormalities amounted to slight weakness of the left side of the face and the left upper limb. The optic fundi were normal. During the next two weeks she had frequent severe headaches, the optic discs developed 2 D. papillœdema, and a few hæmorrhages appeared. The left-sided weakness became more marked and a slight defect in discriminative sense was demonstrated in the left hand. The cerebrospinal fluid pressure was elevated (300 mm.+), and the fluid contained 100 mg. of protein per 100 c.cm., although there was no cellular increase. Radiographs of the skull revealed no definite abnormality.

The evidence suggested an expanding lesion in the right frontal lobe, either a rapidly growing neoplasm, or, because of the relation of the onset of symptoms to an acute febrile illness, an abscess. Mr. Hugh Cairns operated on May 30, 1935, and exposed the right frontal lobe. The convolutions in the lower and posterior part of the frontal lobe were broad and pale, suggesting that the lesion was approaching the surface here, and an incision in the frontal lobe revealed a neoplasm at a depth of 1 cm. from the surface. It had the naked-eye features of a spongioblastoma multiforme. Several portions were removed for histological examination, and sufficient to reduce the intracranial tension. The bone flap was sacrificed, and the scalp closed in the usual manner. Dr. J. G. Greenfield examined the biopsy specimen, and has kindly sent us sections of the tumour. Paraffin sections stained by hæmatoxylin and eosin, hæmatoxylin and van Gieson's mixture, and phosphotungstic-acid hæmatoxylin showed a number of small, irregularly-shaped fragments composed wholly of tumour tissue mixed with blood clot. The tumour was very cellular, and composed of polymorphic cells of various sizes, with indefinite outlines and often separated by a tangle of delicate eosinophil threads. The nuclei of the cells were spheroidal and had a variable chromatin content. Occasional multi- and uninucleate giant cells were present. Mitotic figures were numerous. No definite cytoplasmic fibrils were observed. In places small foci of necrosis were enclosed by palisades of bi-polar cells, and elsewhere similar cells were sometimes orientated towards blood vessels. The tissue as a whole was richly vascular; endothelial proliferation was conspicuous in many of the smaller vessels. The appearances were those of an undifferentiated malignant glioma with the general character of a spongioblastoma multiforme.

Convalescence was uneventful. The wound healed promptly and there was relief from headache. The papillœdema subsided and there was some improvement in the left-sided weakness. On June 24, 1935, she was transferred to the Mount Vernon Hospital, Northwood, Middlesex, under the care of Mr. Stanford Cade, and had a course of radium treatment by a 100 mg. cap applied to the right frontal region: 44,400 mg. hours at 4 cm. skin distance. Desquamation took place over part of the skin flap, but there was a steady improvement in her general health and when she was examined on Aug. 30, 1935, the decompression area was soft, the papillœdema had subsided, and there was only slight weakness of the left side of the face and left upper limb.

She remained well until the middle of January, 1936, when she again began to complain of headaches, and the decompression area became very tense. There was an increase in the left-sided weakness, and it was thought that this deterioration bespoke renewed activity of the tumour. She was readmitted to Mount Vernon Hospital on Feb. 26, 1936, and on this occasion was given a course of high-voltage deep *x*-ray treatment directed to the right frontal lobe (200 kV., 1·5 mm. copper filter; 6,600 r in 17 doses through 5 fields, a.p., 2 lateral, superior vertical). This had the effect of relieving the headache to a considerable extent and reducing the tension of the decompression.

On June 19, 1936, she reported that the headache was getting more severe, and that the decompression was "growing." Indeed the hernia cerebri was larger and tighter than it had ever been, and within the few days which elapsed before she was readmitted to Mount Vernon, she had become drowsy, was vomiting frequently, and had developed a complete paralysis of the left upper limb and a partial paralysis of the left side of the face and the left lower limb.

She then had another course of high-voltage deep *x*-ray treatment (7,800 r through 9 fields, the physical factors as before), and on this occasion there was a dramatic improvement. When she was examined on Oct. 21, 1936, she said that she felt very well. She had had no headache since shortly after beginning the last course of treatment. She was bright and cheerful, and relatives regarded her mentality as normal. The cerebral hernia had diminished until it was flush with the level of the surrounding skull and it was quite soft. The optic discs were flat and visual acuity was normal. There was a slight weakness and sensory defect in the left upper limb, but the facial weakness was hardly

demonstrable and there was no weakness of the lower limb. On March 5, 1937, there was no striking change except that the decompression area was now markedly indrawn. In July, 1937, she had acute appendicitis treated by appendicectomy without any complications. In February, 1938, it was noted that the left upper limb had improved to the point where there was only a little kinetic weakness of the hand and a slight sensory defect confined to the hand. The decompression area was still markedly indrawn. She returned to full work in a shop, and in June, 1939, she was married.

She remained well, and was leading a normal life until September, 1941, when her left leg suddenly gave way as she was coming downstairs. She did not lose consciousness and thought that she had "turned" her ankle, but when she tried to get up she found that the left leg and arm were completely paralysed. They remained so for two or three days and then began to improve slightly. Recovery was, however, far from complete, and when she was seen on Oct. 4, 1941, she was unable to walk unassisted because of spastic weakness of the left lower limb, while the left upper limb was almost completely paralysed. The decompression area was still markedly indrawn. There was no further improvement, but no definite worsening until February, 1942, when she began to have focal epileptic attacks involving the left limbs and left side of the face. She was readmitted to Mount Vernon Hospital on March 16, 1942, and had another course of deep *x*-ray therapy (9,900 r through 5 fields; physical factors as before) to the right frontal region. Except for cessation of the focal epileptic attacks, there was no striking change in her condition, which deteriorated gradually, and she died on July 24, 1942, seven and a quarter years after the onset of symptoms.

MACROSCOPIC EXAMINATION.—The brain with attached dura was received after being hardened in formaldehyde. The right cerebrum was greatly torn and deformed in the preparation of the specimen. Delicate fibrous adhesions united the dura to the lateral aspect of the right posterior frontal region. The leptomeninges were missing from the remainder of the right frontal and parietal lobe to expose an irregular collapsed cavity with soft friable walls involving the whole of the right centrum semiovale with the exception of the tips of the frontal and occipital poles, and the temporal lobe. A narrow zone of subcortical white matter was spared in the posterior frontal and parietal lobes. The softening extended medially to the wall of the lateral ventricle, and partially involved the corpus callosum, fornix, and septum pellucidum. There was no evidence of any residual tumour at the site of the old operation. The cortex here was replaced by firm, granular, greyish-yellow tissue, measuring about 1 cm. in diameter, with a little tougher grey scar tissue flecked with orange pigmentation. No further alteration was found in the brain except slight shrinkage of the right pyramid. The main cerebral arteries were translucent and patent.

MICROSCOPIC EXAMINATION.—Blocks were prepared from two parts of the scarred operation area in the right frontal lobe, from the lateral aspect of the right frontal and occipital poles to include the wall of the cavity in the central white matter, and from the medulla oblongata. Sections were stained with hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, and phosphotungstic-acid hæmatoxylin.

At the *site of the operation scar* the cortex was focally replaced by dense hyaline collagenous tissue and fibrillary neuroglia. The adjacent cortex was greatly fragmented, apparently from post-mortem handling, and was extensively necrotic. Many of the clefts present, both in this necrotic tissue and in the scarred tissue, were filled with fibrin filaments, suggesting that potential spaces at least were present in such areas before death. Diffuse areas of infiltration with neutrophil leucocytes and with large monuclear cells containing iron pigment were also present in the necrosis about the scar-tissue. Many of the smaller perforating blood vessels had undergone fibrinoid necrosis and thrombosis. Perivascular hæmorrhages were present about some of these. In the adjacent areas of cortex unaffected by necrosis there was severe dropsical degeneration of the pyramidal cells. The deep layers of the tissue bordering upon the cavity in the central white matter were extensively altered by necrosis and the deposition of fibrin filaments. There was no evidence of any residual tumour.

In the *frontal and occipital regions* there was everywhere a similar dropsical degeneration of the neurones. A considerable degree of diffuse gliosis was present both in the molecular layer and in the white matter immediately beneath the cortex. There was severe œdema of the white matter accompanied by diffuse patches of rarefaction, breaking down in places into irregularly-shaped cavities in which small groups of foam-cells were occasionally found. In the occipital region the white matter was less severely altered than in the frontal. The margins of the central cavity in the white matter in general showed no reaction indicative of an ante-mortem softening. On the other hand the white matter here was entered by occasional clefts, the walls of which were lined in places with fibrillary glia and groups of plump cells of amœboid appearance. The perforating blood vessels were unaltered save for hyaline, collagenous thickening of a small group in the white matter of the frontal lobe. There was fibrous thickening of the leptomeninges accompanied by a moderate infiltration with large mononuclear cells, apparently derived from the arachnoid.

In the *medulla oblongata* there was slight fibrous thickening of the leptomeninges, with slight lymphocytic infiltration over the pyramids. Beneath the floor of the fourth ventricle a few vessels were cuffed with similar cells. There was partial demyelination with slight atrophy of the right pyramid.

COMMENT.—The most remarkable feature of this case is the proved cure, by combined operative and irradiation treatment, of an example of a highly malignant glioma, spongioblastoma multiforme.

The interpretation of the circumstances leading to the death of the patient is difficult. From the histological appearances of the tissue in the region of the operation area it must be inferred that irradiation necrosis was an important factor: the

recent necrosis both of cortical tissue and of the perforating vessels, and the extensive escape of fibrin into these tissues, are similar to the changes already described in Cases 1 and 2. But the extensive cavitation of the right hemisphere would seem to be most readily explained as a post-mortem effect based perhaps upon a massive œdema and diffuse degeneration of the white matter, of which indeed there is histological evidence. This œdema and degeneration may well have been a more acute effect of irradiation than the necrosis observed in Cases 1 and 2. The normal condition of the main cerebral arteries excludes an alternative explanation in terms of embolism or thrombosis of the right middle cerebral artery.

CASE 4

Unverified right frontal glioma. Bony decompression and x radiation. Sudden left hemiplegia one year after operation. Death. (R.I. 16068/41.)

A man aged 37 was admitted to the Radcliffe Infirmary on June 14, 1941. He had been in good health until two months before admission, when he began to complain of headache, fatigue, occasional vomiting, and a feeling of weakness in the left lower limb. One week before admission he began to have frequent attacks of pins and needles in the left thumb and the dorsum of the left hand, occasionally extending to the left lower lip. There was no loss of consciousness, nor any involuntary movements during these attacks.

On examination he appeared to be a healthy man and the general physical examination revealed no abnormalities. The blood pressure was 130/85 mm. Hg. He was alert and intelligent and, during several days observation in hospital, he had very little headache although the focal sensory attacks continued. Both optic discs were swollen (2D), but the visual fields were full and the acuity of vision was normal. The positive findings amounted to a very slight weakness and clumsiness of the left lower limb, with increased tendon reflexes on the left side, and an extensor plantar response. There was very slight impairment of two-point discrimination and stereognosis in the left hand. The spinal fluid pressure was 180 mm., and the fluid was normal on analysis. Radiographs of the skull revealed no abnormalities. Ventriculography showed a displacement of the ventricular system to the left side, with some elevation of the floor of the right ventricle in the region of the optic thalamus. It was thought that these appearances indicated a diffuse infiltrating tumour of the right cerebral hemisphere, and a fibrillary astrocytoma was considered the most likely possibility. In view of the patient's slight signs and symptoms, it was decided to do only a bony decompression by means of a right postero-lateral osteoplastic flap, without opening the dura, and to follow this with a course of deep *x*-ray treatment. He stood the operation well; there were no new neurological developments and he had no headache or epileptic attacks before his discharge on July 7, 1941.

In August, 1941, he had a course of deep *x*-ray therapy directed to the right parietal region. The dosage was 10,500 r through five fields: anterior, posterior right and left lateral, superior, vertical, 250 kV., 20 m.a. 1·5 mm. copper filter, 21·7 cm. F-S distance. This produced permanent epilation of the right parietal region of the scalp but there was no burning or ulceration.

He returned to work as a bank manager in September, 1941, and was subsequently co-opted by a Government department for an important post as inspector of factories. This he did very well, and he led a normal active life, without any headache or epileptic attacks, until June 10, 1942, when he complained of a slight generalized headache which he attributed to overwork. Three days later he had a fit in the street, and was unconscious for a short time. He was taken to hospital where he soon recovered consciousness, but he was left with a partial paralysis of the left side of the body. Four days after this he had another fit which left him with a complete left hemiplegia, and in this state he was readmitted to the Radcliffe Infirmary on July 4, 1942. He was dull and apathetic but could speak in a slow monotonous whisper and he said that he had no headaches. There was no neck stiffness, and Kernig's sign was absent. He was incontinent of urine and fæces. The right side of the scalp was epilated but there was no ulceration. The bone flap was slightly elevated, and there was a low degree of chronic papillœdema. The spinal fluid pressure was 195 mm. He appeared to have a left homonymous hemianopia, probably complete in the upper quadrant. There was no voluntary movement in the left side of the face, or in the left arm and leg. There was some weakness of the right limbs as well, but this was compatible with his apathetic state and his poor general condition. All the tendon reflexes were exaggerated, the left more than the right. The left plantar response was extensor, the right equivocal. There was marked involuntary grasping in the right hand.

The spinal fluid was clear and colourless, and contained 100 mg. of protein per 100 c.cm. Radiographs of the skull showed no abnormality except the operative defect. At first the electro-encephalogram revealed a condition of subclinical status epilepticus from a diffuse focus in the right fronto-parietal region (when he was admitted), but the only clinical manifestation was a rhythmical twitching of the left calf muscles and an occasional flicker in the muscles of the left arm. When these phenomena ceased, the electrical discharge was less persistent and of lower voltage. Thereafter, occasional transient subclinical attacks could be picked up, followed by a succession of regular 6 per sec. waves. At other times, there was an irregular discharge of low-voltage waves from a shifting focus over the right hemisphere.

He became progressively more stuporose and died in coma on July 19, 1942, one year after operation, eleven months after the *x*-ray therapy, and five weeks after the onset of his final illness.

EXAMINATION OF THE BRAIN.—The inner surface of the dura over the right cerebrum was covered by a tough grey fibrous membrane, up to 0·2 cm. thick, diminishing in thickness towards the occipital pole and not continuing on to the falx. There was moderate fibrous

thickening of the leptomeninges over the corresponding area of the right cerebrum and, less marked, over the vertex of the left cerebrum. About the right Sylvian fissure there was diffuse *café-au-lait* pigmentation. The right frontal lobe was greatly expanded and, on its mesial aspect, nodules of tumour-like tissue projected from the neighbourhood of the frontal pole to indent the opposing surface of the left frontal lobe.

On coronal section the dorso-medial third of the right frontal lobe was greatly expanded, the white matter in this region showing diffuse opaque lemon-yellow necrosis while the adjacent cortex appeared swollen, firm, and unusually pale, especially in the superior frontal convolution and medial aspect of the lobe. The junction of cortex and white matter was rendered conspicuous by a zone of greatly engorged blood vessels and petechial hæmorrhages. The area so involved measured 6 by 4 cm. in the coronal plane and about 9 cm. antero-posteriorly; it extended into the genu of the corpus callosum and caused occlusion and ventral displacement of the frontal horn. The remainder of the white matter of the right frontal lobe was œdematous. No further change was found in the rest of the brain, which was congested.

MICROSCOPIC EXAMINATION.—Blocks were prepared from the thickened dura over the right cerebrum and the right frontal lobe at the site of the supposed tumour. Sections were stained by the same methods as in the preceding cases. Frozen sections of the frontal lobe were stained by a variety of silver techniques.

There was great collagenous thickening of the dura including the inner areolar layer. A few groups of macrophages containing iron pigment were present both in the inner layer and between the collagenous fibres of the outer layers. The included blood vessels were engorged, and in some the lumen was reduced by fibro-muscular thickening of the intima.

Over the right frontal lobe the leptomeninges showed considerable fibrous thickening. Focal collections of fibrin and a good many vacuolated mononuclear cells were present in the interstices. Slight fibrous thickening of the adventitia of some of the meningeal arteries was the only vascular change present. In the cortex there was considerable diffuse loss of the pyramidal cells accompanied by a proliferation of large fibrillary astrocytes. The appearance was similar to that described in Case 1 but the changes were nowhere so advanced: It was diffuse throughout the cortex forming the summits of the gyri and depths of the sulci. Necrosis was limited to minute perivascular foci where the vessels had undergone fibrinoid necrosis and thrombosis. This vascular change was widespread and was often associated with perivascular zones of fibrin filaments, sometimes accompanied by extravasated red corpuscles. The fibrin did not permeate the tissue so widely as in Cases 1 and 2. The adventitial sheaths of some of the perforating vessels were infiltrated with small lymphocytes. A few of the larger vessels showed hyaline collagenous thickening with loss of structural characters in their walls combined with similar infiltration.

Relatively few microglial cells could be recognized in the cortex: most of those present were aggregated as amœboid forms, containing sudanophil lipoid, along the borders of the white matter. At more superficial levels in the cortex attempts at the formation of rod cells appeared in places, but many of these cells were apparently degenerating. Few oligodendroglial cells could be recognized; those present were in stages of acute swelling.

The white matter showed complete necrosis with aggregates of degenerating leucocytes in many places, while fibrinoid necrosis and thrombosis affected many perforating vessels, especially those of smaller calibre. Again some of the larger vessels had undergone collagenous thickening with the production of anastomosing leashes of reticulin fibres in the adjacent neural tissue, as seen in Case 1. There was advanced fragmentation of the axis-cylinders.

COMMENT.—In this case, which was studied before any other in this series and at a time, therefore, when we were unacquainted with the effects upon the brain of intensive irradiation, the appearances seen in the right frontal lobe were interpreted as an unusual kind of glioma. To the naked eye it was not unlike some forms of spongioblastoma multiforme. Under the microscope, however, it was clearly of a different character. Provisionally it was thought that the tumour might be a diffuse astrocytoma in which massive subcortical necrosis had been induced by irradiation. In retrospect this diagnosis was supported by the presence of nodular projections from the medial surface of the frontal pole, which might not reasonably be expected in the region of an uncomplicated necrosis of brain tissue. On the other hand the histology was so closely similar to that of Cases 1 and 2 that the possibility has to be entertained that the whole of the area described in this case was of the same character. In this event the precise location of the original tumour and its ultimate fate remained undecided.

CASE 5

Focal epilepsy due to left frontal astrocytoma. Decompression. Radiation treatment. Deterioration three years later. Re-exploration and removal of necrotic mass from left frontal lobe. Recovery. (R.I. 20806/42.)

A woman aged 20 came under observation on Jan. 2, 1942, suffering from focal epilepsy. She was a normal child until at the age of 11 years she was struck on the forehead by a cricket bat. She was dazed, but not unconscious, and nothing was thought of this injury until four months afterwards when she had a succession of attacks of aphasia lasting a few minutes at a time. Two months later the character of the attacks altered: they were ushered in by aphasia (inability to express herself, although she seemed to know what she wanted to say); then the right side of the face, right arm and leg would begin to twitch convulsively, in that order. In some of the attacks she lost consciousness for a few minutes and was dazed for half an hour afterwards. In

others there was no loss of consciousness. These attacks recurred at irregular intervals but she was rarely free for longer than two months. In the intervals between the attacks she was quite well. She had no headache except for a short time after each attack.

On examination she was seen to be a healthy-looking young woman, and speech and intellect were normal. The optic fundi were normal and the spinal fluid pressure was 85 mm. The neurological examination revealed a very slight weakness of the right side of the face and of the right arm and leg, but there was no difference in the tendon reflexes and both plantar responses were flexor. There was no sensory disturbance. Radiographs of the skull showed a small calcified nodule in the left frontal lobe and the electro-encephalogram revealed a focus of abnormal activity in the same region. A cisternal encephalogram showed a slight displacement of the anterior part of the ventricular system to the right side.

It was thought that the length of the history, the presence and character of the calcification, and the ventriculographic appearances indicated an infiltrating astrocytoma in the left frontal lobe. On Feb. 20, 1942, a left frontal osteoplastic flap was reflected. It was decided to limit the operation to a bony decompression. The dura was not opened, but through it the convolutions in the frontal lobe could be seen to be broadened and pale. To prevent the bone flap from uniting, strips of gutta percha were inserted between the bony edges. She stood the operation well and on March 14, 1942 was sent to Mount Vernon Hospital for a course of deep *x*-ray treatment. This produced permanent epilation of the left frontal region, and there was no definite effect on the character and frequency of the fits.

She was seen at regular intervals thereafter and remained in much the same state until about June, 1945, when she began to deteriorate: the fits became more frequent and severe, and she developed progressive aphasia and progressive weakness of the right arm and leg. She was slower mentally, and complained of a good deal of headache. There was no definite papill-œdema, but in addition to moderate aphasia and right hemiparesis there was now some disturbance of sensation in the right upper limb, light touch and stereognostic sense being particularly affected.

The left frontal region was explored again on Feb. 21, 1946. The scalp was thin and relatively avascular. It was tightly adherent to the bone flap, but the gutta percha strips had prevented any union of the bone flap to the skull. The bone flap looked dull and white and it too was avascular with areas of rarefaction visible on its surface. The dura was milky white and thickened, but was not adherent to the brain. The arachnoid over the exposed frontal lobe was less translucent than normal, but the blood vessels on the surface looked quite normal. The convolutions of the exposed brain all looked a little broader than normal, and the middle frontal one in particular was about 2 cm. in width and felt very firm to the touch, whereas the others felt soft. A portion of the frontal lobe was excised including the superior and middle frontal convolutions, extending 7·5 cm. from before back by 6 cm. from side to side, by 4 cm. deep. It weighed 66 g. The subcortical white matter was very soft, and had a slightly yellowish tinge. In some places there were firm strands of whitish tissue extending from the main mass out into the surrounding white matter. No definite neoplastic tissue was seen. The brain was quite slack after the removal of this mass, and the dura was closed completely, the bone flap replaced, and the scalp closed in the usual manner. The wound healed normally and convalescence was uneventful. There was a transient exacerbation of the aphasia and right-sided weakness following operation, but this improved rapidly and by the time the patient was discharged on March 10, 1946, the neurological status was virtually the same as on admission. Subsequently she improved in every respect but when last seen in April, 1947, she was still having attacks.

MICROSCOPIC EXAMINATION.—Microscopic examination of the specimen removed at operation revealed a superficial circumscribed wedge of dense collagenous tissue, embedded in which were numerous islands of glial tissue composed for the most part of bipolar fibrillary astrocytes. The highly cellular character of these islands suggested that they might represent residual tumour tissue. The adjacent convolutions were free from tumour; in places they appeared normal save for œdema and variable degrees of neuronal chromatolysis, but elsewhere they displayed conspicuous necroses, hæmorrhages, and vascular changes identical with those that have been described in detail in Case 1.

Discussion

We believe that the necrotic lesions which occurred in these cases were due to radiation treatment. We have not encountered similar lesions in untreated cases, and there is nothing to suggest that the primary disease for which the treatment was given would predispose to such necrosis: many cases of brain tumour treated by various surgical methods have been examined and no comparable effects have been observed; nor is there any evidence that pre-existing vascular disease contributed to these effects, as in each case the vascular system was normal as assessed by clinical standards and in three cases by necropsy examination.

There are other reports in the literature of similar effects following radiation treatment in human subjects. Fischer and Holfelder (1930) described the case of a patient who had received radiation treatment for a rodent ulcer of the scalp and who seven years later developed focal epilepsy referable to the irradiated site. Biopsy examination revealed destruction of cortical architecture, œdema of interstitial tissue, thickening of intracerebral blood vessels, a "structureless substance resembling hyaline or amyloid" around the vessels, and numerous old hæmorrhages and necroses. These changes are similar to those described in Case 1 of this report. Markiewicz (1935) reported a similar case although the interval between radiation

and the onset of symptoms was shorter (eighteen months). Scholz and Hsu (1938) described the changes found in the brains of two deteriorated schizophrenic patients who had been irradiated experimentally eighteen months before death. Their mental state was apparently unaffected, but their general health failed gradually and they became bed-ridden shortly before death. No neurological abnormalities were observed, possibly because of the difficulty of examining such patients. The pathological findings were very similar to those described above, and a photograph of their first case presents much the same appearance as that observed at operation in our Case 1. O'Connell and Brunschwig (1937) observed diffuse degenerative changes in the brains of three patients who had received intensive radiation treatment for intracranial gliomata. They emphasized particularly the effect on normal nerve cells, neuroglia, and microglia, and regarded the changes seen in the blood vessels as of secondary importance. Although their cases had received tumour doses of between 12,000 and 14,000 r (more than most of our cases), the changes which they describe do not seem to have approached the necrosis which occurred in our cases, nor from their report does it seem that the degeneration had any focal distribution, since it occurred widely throughout the brain.

Stevenson and Eckhardt (1945) have described a case of tetraplegia and respiratory paralysis in the spinal cord due to necrosis of the cervical cord after radiation treatment for malignant glands in the neck.

Similar effects have been observed in experimental animals. Lyman and others (1933) irradiated the occipital region of four dogs, three of which were killed within six weeks to study early changes which might be referable to radiation. The fourth animal was killed six months after radiation; in the first five months there were minor alterations in behaviour but no gross physical abnormalities were apparent. Thereafter the animal deteriorated rapidly, showing ataxy, weakness of the limbs, torpor, blindness, and sphincter paralysis. This rapid terminal collapse was in some ways comparable with the clinical course of our Cases 2, 3, and 4. Examination of the brain showed extensive necrosis, maximal in the irradiated field, with degenerative changes in the capillaries and precapillaries, and severe hyaline degeneration and obliterating sclerosis of arterioles. These workers concluded that the harmful effects of radiation were directly referable to changes set up in the blood vessels. On the other hand, Davidoff and others (1938) irradiated a series of monkeys and in some of them produced multiple areas of cavitation with little glial reaction and minimal changes in blood vessels. They regarded these as direct effects of radiation on the parenchyma rather than as the result of vascular lesions. These authors remarked that there may be an interval of four to six months between the radiation treatment and the clinical manifestations of harmful effects. Some years earlier Paterson Ross (1931) produced local necroses in rabbit's brains by implanting radon seeds and radium needles in doses considerably exceeding those employed in therapy. Using smaller doses, he found local degenerative changes in nerve cells and neuroglia, short of necrosis, and although he says that the earliest recognizable response to radiation was in the vascular endothelium, and that hæmorrhage and thrombosis might occur later, he regards the effect on the parenchymatous elements as of major importance.

On the whole our evidence favours the view that the primary effect of radiation is on the smaller blood vessels. The long latent period which may elapse after radiation suggests that the radiation initiates a progressive change in the smaller blood vessels which has the effect of diminishing their lumen, although this may not reach a critical level for many months or years. If the resulting ischæmia is gradual, there would probably be a slowly progressive loss of function, as in Case 2. If the ischæmia developed rapidly, as by thrombosis in already affected vessels, there would probably be sudden manifestations as in Cases 3 and 4. It seems unlikely that a progressive effect on nerve cells would so long delay clinical manifestations: thus Case 4 was free from symptoms and functionally normal until ten months after radiation and five weeks before death. It may be that there are primary parenchymatous changes which are masked by later vascular lesions, but in the three dogs studied by Lyman and others within six weeks of radiation, the predominant changes were in the smaller blood vessels rather than in the nervous parenchyma.

We have no exact means of determining the incidence of this effect. Three of the cases described above and two others were drawn from a group of 113 patients who had received radiation treatment. We suspect that it is even more common than we have found, because several patients have died in circumstances similar to those we have described, but necropsy examination has not been possible. In other cases massive necrosis of the tumour tissue, usually spongioblastoma multiforme, has been found; but inasmuch as such necrosis is a usual feature in untreated cases it has proved impossible to assess whether it is due to the irradiation. It is probable, too, that many patients who have received radiation treatment for brain tumours

die from the effects of the tumour before necrotic lesions have had time to develop.

Our purpose in reporting these cases is to call attention to a harmful effect of radiation therapy which if not frequent is by no means rare, and to suggest that a review of current dosages and technique is necessary. Knowledge of the clinical features may explain some problems which have arisen in the past and will continue to face the clinician who is interested in the after-treatment of patients with brain tumours subjected to radiation. Thus a recurrence or aggravation of symptoms is usually regarded as being due to increased growth of the tumour, and that explanation is undoubtedly correct in the majority of cases. Sudden episodes are usually regarded as being the result of hæmorrhage into the tumour, but in our experience this is a rare occurrence. In both groups, the possibility of radiation necrosis should be borne in mind. Although, as in Case 5, it may be necessary to explore the irradiated area before the diagnosis can be established, this would at least prevent further damage being done by subsequent courses of radiation.

The adjustment of dosage and technique is a matter for further investigation by the physicist, radiotherapist, and experimental pathologist. By present standards, the dosage employed in our cases was heavy but not excessive, and none of them had significant damage to the scalp or skull. Nevertheless it is obvious that the effect on the brain may be so damaging that any beneficial effect on the tumour is eclipsed. It remains to be discovered how much radiation the brain will tolerate without necrosis, and—having determined that—to find out whether this upper limit of safety is still effective against the tumour. We do not intend to decry this method of treatment, because with many brain tumours, notably of the glioma group, we think that radiation in conjunction with surgery has a contribution to make : Case 3 represents the longest survival period of any verified tumour of the spongioblastoma multiforme type that we have encountered, and its disappearance must be attributed to the radiation treatment. Yet we feel that the present technique is uncertain enough in its effects to demand that radiation treatment be given only to verified tumours which are not amenable to surgery and for which no further operation is contemplated.

Summary

1. The clinical and pathological features of five cases of necrosis of the brain following radiation therapy are reported.

2. These cases were treated in different centres with accepted techniques and dosages.

3. The clinical effects may come on suddenly, progress to a point, and become arrested ; or they may come on gradually and lead to death.

4. In each case there was a long latent period between the radiation treatment and the onset of clinical signs of necrosis. The shortest interval was nine months, the longest five years.

5. The pathology of the necrosis appears to be related to reactions in the smaller blood vessels, in which collagenous thickening, fibrinoid necrosis, and thrombosis are conspicuous.

6. As it seems impossible to predict in which cases necrosis will occur, it is suggested that radiation should be reserved for inoperable tumours and those cases in which no further surgical procedures are contemplated.

REFERENCES

Davidoff, L. M., Dyke, C. G., Elsberg, C. A., and Tarlov, I. M. (1938). *Radiology*, **31**, 451.

Fischer, A. W., and Holfelder, H. (1930). *Dtsch. Z. Chir.*, **227**, 475.

Lyman, R. S., Kupalov, P. S., and Scholz, W. (1933). *Arch. Neurol. Psychiat., Chicago*, **29**, 56.

Markiewicz, T. (1935). *Z. ges. Neurol. Psychiat.*, **152**, 548.

O'Connell, J. E. A., and Brunschwig, A. (1937). *Brain*, **60**, 230.

Paterson Ross, J. (1931). *Brit. J. Surg.*, **18**, 618.

Scholz, W., and Hsu, Y. K. (1938). *Arch. Neurol. Psychiat., Chicago*, **40**, 928.

Stevenson, L. D., and Eckhardt, R. E. (1945). *Arch. Path.*, **39**, 109.

HÆMANGIOMAS INVOLVING THE SPINAL EPIDURAL SPACE

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Introduction

The purpose of the present communication is to collect as completely as possible the sources of information relating to a rare group of tumours of the spinal epidural space—those of blood-vessel origin*—and to record eight previously unpublished examples of this condition. It has been thought helpful to include in the study not only those tumours which arise primarily within the epidural tissue itself, but also those which extend into or invade the epidural space from an adjacent vertebra; for as the analysis of the known cases proceeded, it became obvious that there were intermediate stages between the purely epidural and the purely vertebral hæmangioma.

The frequency of occurrence of any rare condition is always hard to estimate, and few writers have seen more than one or two epidural hæmangiomas. However, Rassmussen and others (1940) mention the occurrence of twenty-eight epidural tumours of blood-vessel origin among 557 intra-spinal neoplasms in the records of the Mayo Clinic; and Elsberg (1941) found four in his personal series of eighty-five epidural tumours of the spine.

Purely epidural hæmangiomas seem almost always to occur in the thoracic spine. In histological structure they vary from cavernous hæmangiomas to the less mature hæmangioendotheliomas and hæmangioblastomas, some of which latter have shown a tendency to spread through the intervertebral foramina into the extraspinal tissues and to recur locally after removal. Reference to the literature has revealed fourteen authenticated examples of epidural hæmangioma of mature type (Liebscher, 1901; Devic and Tolot, 1906; Bériel, 1922; Balado and Morea, 1927; Rand, 1927 (Case 1); Petit-Dutaillis and Christophe, 1931; Bucy, 1932; Mixter, 1932 (Case 6); Johnston, 1938; Elsberg, 1941 (2 cases); López Ibor and Peraita, 1941; Wyburn-Mason, 1943 (Case 46); Grapiolo and Morea, 1944). Bériel's (1922) case was further discussed by Cornil and Mosinger (1932), but these writers did not, as has sometimes been stated, bring forward any new examples. Wyburn-Mason (1943) cited as Cases 47 and 48 in his monograph two further examples observed by Professor Dott at Edinburgh, but without giving any details. This, however, is evidently a misunderstanding (Dott, 1947), and the only example of a mature epidural hæmangioma seen at Professor Dott's Clinic is now by permission published for the first time below (Case 1). Two other examples, one from Mr. W. R. Henderson's Clinic at Leeds, and one from Mr. A. Sutcliffe Kerr at Liverpool, are also published with their permission (Cases 6 and 8), thus raising the total number of recorded cases of purely epidural hæmangioma to seventeen.

Less mature tumours, hæmangioendotheliomas and hæmangioblastomas, have been reported by Dandy (1925), Naffziger and Brown (1933; 3 cases), P. Guillain (1933), Kaplan (1935, 1942), Elsberg (1941), and Wyburn-Mason (1943; Cases 62 to 65). Wyburn-Mason, again evidently by misunderstanding, also refers to two examples seen by Professor Dott and numbers them in his monograph as Cases 56 and 57, but in fact Professor Dott has only seen one example (Dott, 1947) which is now published by permission below (Case 2), together with a recent case from this department (Case 5). The number of authenticated cases of epidural hæmangioendothelioma or hæmangioblastoma is therefore fourteen.

It may be added that all these tumours except one (Wyburn-Mason's Case 63) occurred in the thoracic spine and that several cases of predominantly mature tumours were noticed to show here and there some blood vessels of new formation (which incidentally justifies their description as tumours rather than as telangiectases).

Finally there are those blood-vessel tumours of the vertebræ themselves, which are associated with epidural hæmangiomas as well. Some reference to the recorded cases will be made below. It is inter-

* The interested reader may also consult the important reviews of Globus and Doshay (1929), Antoni (1936), and Turner and Kernohan (1941).

esting that although only three-fifths of the 579 cases of vertebral hæmangioma examined in Schmorl's laboratory occurred in the thoracic spine (Junghanns, 1932a), yet proved epidural extensions of vertebral hæmangiomas have been found only in the thoracic region. Vertebral hæmangiomas themselves are almost always mature in type, but a case of hæmangio-endothelioma of the vertebra with an epidural extension is recorded here (Case 3). The others, Cases 4 and 7, are both of a mature vertebral hæmangioma with a histologically similar epidural extension.

Epidural metastases from primary malignant blood-vessel tumours occurring elsewhere in the body have occasionally been recorded (Shenkin and others, 1945), but no examples occurred in the present series.

Case Reports

Case 1 : Epidural Hæmangioma.—A woman of 37 gave a history of pain in the back for nine months with a more recent onset of fairly severe paraplegia. At operation (1925) by Professor Dott, she was found to have an angio-lipoma of the epidural space extending from the second to the sixth thoracic vertebræ and dipping into the intervertebral foramina. It was completely removed (Fig 1). Microscopic examination showed a cavernous hæmangioma with a very fine connective-tissue stroma containing fat cells (Fig. 2). The patient made a good recovery but with considerable residual spasticity. This spasticity disappeared dramatically nearly four years later after an attack of influenza, and when last seen in 1932 she had remained very well.

Case 2 : Epidural Hæmangioendothelioma.—A man of 39 was first seen in December, 1929. He gave an eight-week history of root pains at the level of the eighth thoracic nerves, followed by progressive paraplegia. At operation by Professor Dott a localized tumour was removed from the epidural space at the expected level. Histological examination of it showed a hæmangioendothelioma with pronounced extravascular endothelial cell development and marked hyaline change around some of the vessels. The patient unfortunately died of pulmonary embolism eight days after the operation.

Case 3 : Epidural and Vertebral Hæmangioendothelioma.—A girl aged 17 was admitted to Professor Jefferson's neurosurgical unit at Manchester Royal Infirmary on Oct. 5, 1942, with a history of gradual onset of weakness of both legs which had commenced six months before. She had not walked for four months. Six weeks before admission she began to feel " pins and needles " in both legs. She had noticed no sphincter disturbance. Pain in the back was very slight.

EXAMINATION.—The patient was a healthy-looking girl and, except for acne vulgaris of the face and back, was of normal physique. There was some hypalgesia below the tenth thoracic nerves on both sides, becoming more marked below the knees and without sacral sparing. Vibration sense was impaired in both legs, and position sense diminished at the right ankle and in the toes of both feet. The abdominal reflexes were absent.

There was marked spasticity and diminution of voluntary power in all muscle groups of both legs, the left leg being more affected than the right. Tendon reflexes in the legs were all exaggerated and ankle clonus was present on the left side. The left plantar response was pathological, the right absent. *X*-ray examination showed typical hæmangiomatous changes in the tenth thoracic vertebra (Fig. 5).

Lumbar puncture was not performed because of the acne of the skin of the lower back, and operation was deferred for some weeks on the same account.

OPERATION.—When Professor Jefferson operated on Oct. 29, 1942, the spines and laminæ of the ninth to the eleventh thoracic vertebræ were exposed and removed. The lamina of the tenth thoracic vertebra was abnormally hard and vascular, and when it had been removed there was found to be a localized excess of firm epidural tissue beneath, through which coursed large venous channels. This epidural tissue was removed piecemeal, whereupon the dura itself was found to be pulsating normally and it was not opened. The wound was closed in the usual manner.

The operative specimen was submitted to Dr. E. Pollak of the University Department of Neuropathology at Manchester Royal Infirmary, who reported as follows on its microscopical appearance :

" Small bits of bone and of infiltrated soft tissue have been submitted. The bone itself shows various signs of destruction : the finer lamellar structure is disturbed, and osteoclastic activity is visible everywhere. Between the splinters of bone there are islands of neoplastic tissue filled with more or less differentiated vascular formations. The infiltrated soft tissue comprising the epidural part of the tumour shows in some places very obvious dedifferentiation with little formation of mature blood-vessel tissue. On the other hand there are areas elsewhere of a higher degree of differentiation where the vessels are well formed and filled with blood vessels, while the walls themselves are often thick and rather cellular in their structure. The calibre of the vessels varies, and in places there is a very dense vascular pattern with more or less interstitial tissue, the cells of which are mostly endothelial (Figs. 3 and 4). The histological diagnosis is of hæmangioendothelioma of the spine and epidural space."

The patient made a good recovery from this intervention, and when transferred to Christie Hospital, Manchester, for deep *x*-ray therapy a month later she was somewhat improved, with less spasticity. Ankle clonus was no longer present and power was augmented, especially at the ankle joints.

When seen again in July, 1943, she was back at work in a factory. By this time her tendon reflexes were no longer exaggerated and both plantar responses were flexor, but the left leg was still weak, and appreciation of pin-prick was not quite normal below the knees. *X*-ray examination showed no alteration of the hæmangiomatous vertebra.

The patient's last visit was in July, 1947. She then reported that in 1944 she had had to give up her work because there was a lot of standing and running about to

be done, and her left leg had let her down several times in a couple of months. Shortly after this, however, she had got married, and was now able to do a full day's housework without any pain in the back or weakness of the legs. She could walk two miles comfortably. On examination she was found to be in very good general condition with a normal range of back movements. The gait was normal, and there was no objective weakness in any muscle group of either leg. There was slight subjective hypoalgesia in the right leg in the area of the second lumbar to the first sacral dermatomes. Other modalities of sensation were perfectly preserved. Sphincter control was reported to be quite normal. *X*-ray examination showed a slight increase in density of the body of the tenth thoracic vertebra but no other change (Fig. 6) from the situation revealed five years before.

Case 4: Vertebral and Epidural Hæmangioma.—A woman aged 34 was referred from the Maternity Unit at St. Mary's Hospital, Manchester, on Dec. 21, 1946, in the thirty-sixth week of her third pregnancy. She stated that her first pregnancy had been uneventful, but that in 1943, towards the end of her second pregnancy, she had been troubled by severe girdle pains round the lower chest. These pains, however, had disappeared five days before labour and she had thought no more about them. In the thirty-second week of her present pregnancy the same pains had started again. She had found relief from standing up, but had been made worse by lying flat, stooping, or coughing. She said that she had often had to get up and walk about the room at night to ease the pains.

Two weeks later her legs began to feel numb and cold, and to tingle. Simultaneously the left leg seemed to lose power, to be followed by the right leg in the next few days. Ten days before admission she had barely been able to walk half a mile, and five days after this she had been able to do her housework only by dragging herself from one piece of furniture to the next. Finally that same day she collapsed on her bed and could not get up at all. Next day she developed dribbling incontinence of urine and noticed that she was beginning to pass flatus if she coughed or tried to sit up. The girdle pains in the chest were by now very severe indeed and associated with a slight ache between her shoulder-blades.

EXAMINATION.—The patient was a tall, obese woman. There was a 36-weeks' pregnancy, the presentation being by the breech. Below the level of the sixth thoracic dermatome there was complete loss of posterior column sense, and pin-prick was appreciated either as blunt or occasionally as a diffuse tingling. There was no sacral sparing. Light touch was slightly impaired in the left thigh and below both knees, but was normal elsewhere. Abdominal and anal reflexes were absent. The abdominal muscles were paralysed.

Both legs were very spastic, with bilateral clonus at knee and ankle and extensor plantar responses. There was weak action against gravity in all muscles of the right leg, but in the left voluntary movement was only detected in the glutæi and the adductors of the thigh, and occasional flexor spasms occurred. Sphincter control was quite absent.

Lumbar puncture showed a pressure of 60 mm. There was a complete block to Queckenstedt's test but a slow rise and fall on abdominal compression. The fluid showed 120 mg. of total protein per 100 c.cm. and a slight increase in globulin. It was clear and colourless and contained 2 leucocytes per c.mm.

Radiographs of the thoracic spine showed no gross bony abnormality, but the examination was difficult because of the patient's size and pregnancy, and the resultant pictures were not entirely satisfactory.

A preoperative diagnosis of intraspinal hæmangioma was made.

OPERATION.—At operation on Dec. 21, 1946, by Professor Jefferson, the spines and laminæ of the fourth to sixth thoracic vertebræ were exposed. It was noticed that the bone itself was harder than normal and bled very profusely. Eventually the laminæ were removed and the whole of the epidural space was seen to be covered by a network of huge tortuous veins, two of which burst spontaneously. Under the circumstances no biopsy of the epidural tissue could be made, but the diagnosis of hæmangioma was obvious. After hæmorrhage had been arrested with fibrin foam the wound was closed.

Immediately after this intervention the patient's neurological condition was unchanged. On Dec. 26 she went into labour and was transferred back to St. Mary's Hospital, Manchester, where she was delivered spontaneously of a healthy male child weighing 7½ lb. The next day she developed acute dilatation of the stomach, collapsed suddenly, and died in the early hours of Dec. 28.

Only a very limited autopsy was permitted, but Dr. Pollak reported as follows on a specimen of bone obtained at operation and on some pieces of epidural tissue removed post mortem.

"The vertebra itself is invaded by a tumour of the hæmangiomatous type (Fig. 7). Spicules of lamellar bone are filled with islands of tumour tissue, the bone is undergoing some degeneration, and osteoclastic activity is very pronounced. The blood-vessel tumour is very well differentiated in appearance, the bony canals being filled with large blood vessels which are dilated, thin-walled, and stuffed with erythrocytes. The overlying epidural tissue shows a tumour which is in the main similar, though here and there are areas of a less differentiated character in which the number of endothelial cells is much greater than in the main mass of the neoplasm (Fig. 8). The spinal cord presents extensive degenerative changes, especially in the white matter, with swelling of the axons and degeneration of the myelin, but no true necrosis of a transverse type. No hæmangiomatous changes can be seen. The histological diagnosis is of hæmangioma of the spine and epidural space."

Case 5: Epidural Hæmangioblastoma.—A 46-year-old plumber was admitted on June 12, 1946. He gave a two months' history of a feeling of pins and needles radiating from the lumbar region down the left leg. Within a few days the left leg, and then the right, had started to become weak. Early in June he had gone to bed one night and woken up to find his legs so weak that

he could no longer stand, and within another seven days he had lost all movement and sensation in both legs. Meanwhile he was finding difficulty in micturition, but without any episodes of acute retention. There was no complaint of pain in the back at any time.

EXAMINATION.—Back movements were full and painless. There was a complete loss of all function below the seventh thoracic segment on both sides, except that there was a trace of urethral and rectal sensation and of sphincter control. Flexor spasms occurred frequently in both legs. There were extensive third-degree sacral-pressure sores.

X-ray examination of the spine showed no definite abnormality. Lumbar puncture revealed a pressure of 160 mm. with a block to Queckenstedt's test and a protein content of 250 mg. per 100 c.cm. There was no increase in cell count and the Wassermann reaction was negative.

OPERATION.—Operation had to be postponed for many weeks because of the severe pressure sores. It was eventually performed on Oct. 31, 1946, by Mr. F. K. Kessel. A laminectomy of the seventh to tenth thoracic vertebræ was performed. The epidural space contained a greyish-red tumour 1 cm. thick apparently completely surrounding the dura. The dorsal part of this tumour was completely removed but its anterior limit could not be accurately established owing to hæmorrhage and the difficulty of access. However, the cord was now found to be pulsating normally within the dura, which was accordingly not opened, the wound being reformed in layers.

Dr. Pollak reported on the specimen of tumour removed :

"The tissue submitted consists of a tumour which extends into the epidural fat. The main bulk of the neoplasm is formed by more or less differentiated elements of blood-vessel tissue. There are some areas, however, where no proper differentiation of vessels occurs and the whole field is occupied by cells of endothelial character (Fig. 9). Mixed with areas of this type are other fields where lumina of vessels are recognizable, lumina partly filled with blood cells, partly empty. Where the tumour extends into the epidural fatty tissue, it is much more differentiated and there are hardly any islands of dedifferentiated neoplasm. The number of blood vessels there is very much increased and their walls are much thicker than normal (Fig. 10). The histological diagnosis is of epidural hæmangioblastoma."

Neurological recovery after this intervention was extremely slow, although a lumbar puncture performed on Nov. 19, 1946, showed no block to Queckenstedt's test. A course of deep *x*-ray therapy was given later in the same month, but without any dramatic benefit. By January, 1947, however, the patient had regained some appreciation of deep pressure and pin prick on both legs, and six months later he had just sufficient voluntary power in his legs to be able to stand while holding on to a fixed bar in the gymnasium. At the time of writing he has regained control over the right foot and toes, and no longer has any difficulty in initiating the act of micturition, but the left leg is still very weak and spastic.

Case 6 : Epidural Hæmangioma.—A woman of 58 was first seen by Mr. W. R. Henderson at the General Infirmary at Leeds on Dec. 31, 1946. Six months before she had a sensation of numbness and tingling on the front of the right thigh, which gradually spread down to the right foot and into the left foot as well. Two months later the same sensations extended up to the lower abdomen, and a month later still she found that she had to walk more slowly than was her habit.

Three months ago this difficulty in walking, which was by now associated with considerable stiffness of both legs, began to get rapidly worse and she found she was no longer able to walk for more than twenty minutes at a time, and she became very tired if she stood for long. For the three weeks before the consultation she had been kept in bed, with some resultant diminution in the numbness of the abdomen and legs.

There was a slight degree of hesitancy of micturition but no other sphincter disturbances. A history of a period of diplopia lasting three weeks and occurring fourteen years ago was elicited, but there was no suggestion of previous trouble with the legs or of mistiness of vision.

EXAMINATION.—There were no neurological abnormalities in the cranial nerves or arms. The abdominal reflexes were all absent but there was no sensory level on the trunk. There was no tenderness or deformity of the spine.

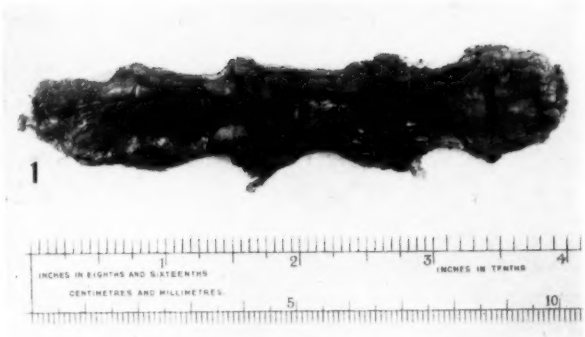
In the legs there was some increase in tone of the proximal muscles, more on the right than the left, with a sustained patellar clonus on the right side. Distally there was some weakness of the ankles and more of the toes, with marked impairment of the appreciation of joint movements and tuning fork as high as the ankles. The gait was spastic and the patient could hardly raise herself on her toes. *X*-ray examination of the spine was negative.

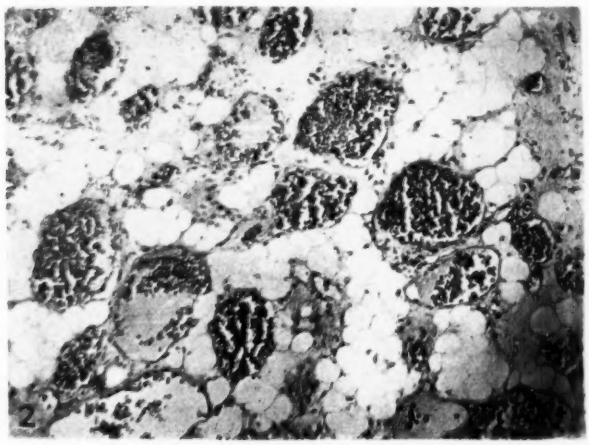
Lumbar puncture three weeks before had shown a pressure of 145 mm. with a free rise (to over 300 mm.) on jugular compression, but the pressure then fell only to 245 mm. The cerebrospinal fluid contained 250 mg. of protein per 100 c.cm. and 5 leucocytes per c.mm. At the present examination it showed a pressure of 60 mm. with no rise at all on jugular compression.

Myelography was then performed by the lumbar route. It showed a complete arrest of the opaque medium at the level of the sixth to the seventh thoracic vertebræ, and exploration was accordingly resolved upon.

OPERATION.—At operation on Jan. 7, 1947, by Mr. W. R. Henderson, the spines of six and the laminæ of five vertebræ were removed through an incision centering on the sixth thoracic spine, the bone appearing normal. This revealed a well encapsulated, dark red, lobulated swelling, measuring $6 \times 2 \times 1$ cm., lying in the dorsal part of the epidural space and extending from the fifth to the seventh thoracic vertebra. It tended to extend into the epidural foramina (cf. Case 1), and received several large veins from the deep surface of the laminæ overlying it.

This tumour was completely removed from the underlying dura, from which it could be separated by blunt dissection. After some rather brisk hæmorrhage from enlarged veins near the intervertebral foramina had





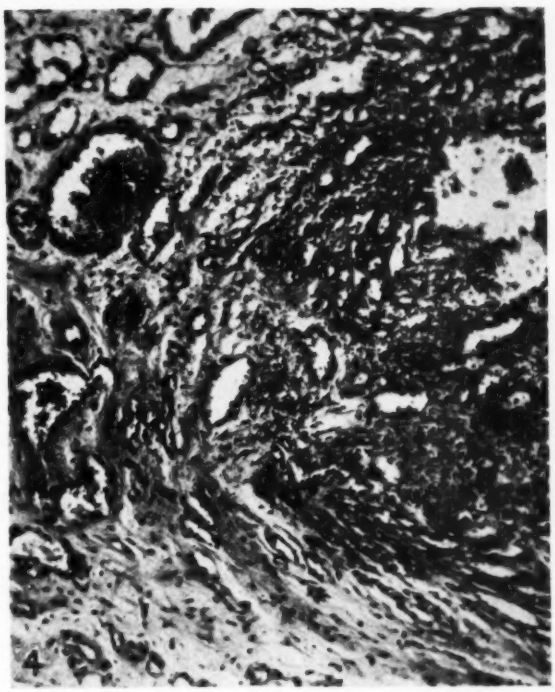


FIG. 1.—Case 1. Specimen removed at operation. Note the lateral extensions of the tumour, corresponding to the sites of the intervertebral foramina.

FIG. 2.—Case 1. Low-power microphotograph, showing typical large blood-spaces with intervening fatty tissue. Hæmatoxylin and eosin.

FIG. 3.—Case 3. A portion of the epidural tissue adjacent to the hæmangiomatous vertebra. Above are well formed, thick-walled blood vessels; below, a less differentiated area. Hæmatoxylin and eosin. ×45.

FIG. 4.—Case 3. High-power view of part of the same field. Hæmatoxylin and eosin. ×110.

FIG. 5.—Case 3. Preoperative *x*-ray appearance, October, 1942. The tenth thoracic vertebra is slightly expanded and shows the striations typical of a hæmangioma.

FIG. 6.—Case 3. *X*-ray appearance, October, 1947. There is slightly increased density of the body of the tenth thoracic vertebra.

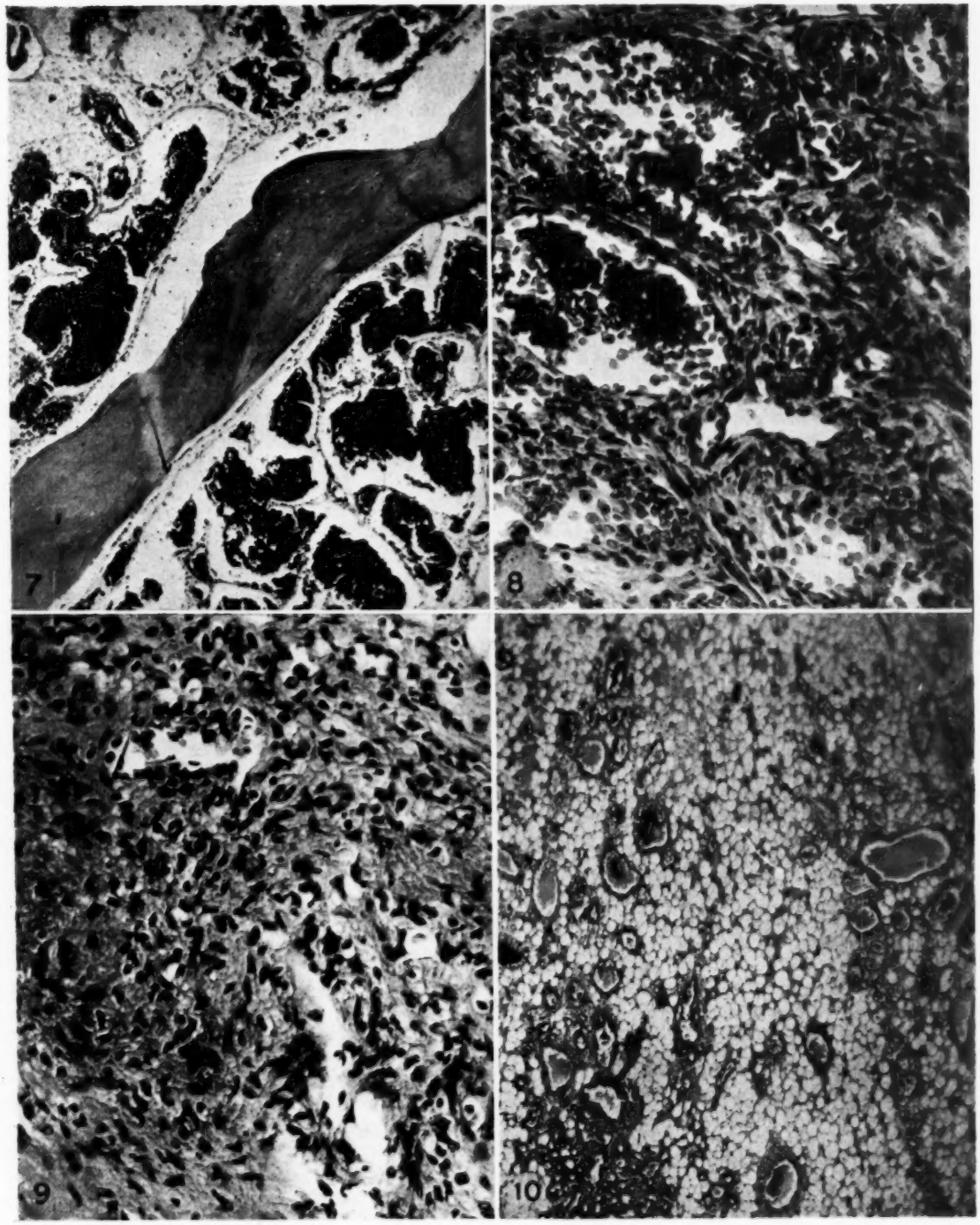


FIG. 7.—Case 4. A section of part of the body of the fourth thoracic vertebra, showing a bony trabecula surrounded by hæmangiomatous tissue. Hæmatoxylin and eosin, ×60.
FIG. 8.—Case 4. An area of epidural tissue in which there is proliferation of endothelial cells around the blood vessels. Hæmatoxylin and eosin, ×160.
FIG. 9.—Case 5. An area of endothelial cells has completely replaced the normal epidural fat. Hæmatoxylin and eosin, ×280.
FIG. 10.—Case 5. Enlarged, thick-walled blood vessels at the edge of the tumour. Contrast these with the thin-walled blood spaces shown in Fig. 2. Hæmatoxylin and eosin, ×20.

been controlled, the wound was closed in the usual manner.

Three weeks after the operation myelography was again carried out, as the opaque medium had not been removed at the time of operation. This time there was no hold-up. A week later the patient was able to return home. There was little change in the objective neurological signs but she reported a gratifying disappearance of the feeling of numbness and tingling in the trunk and of stiffness in the legs.

The pathological report on the operative specimen was as follows :

" This tumour is made up of large numbers of endothelial lined spaces, mainly in contiguity with one another, but otherwise separated by adipose tissue. The spaces are filled with red blood cells. The histological diagnosis is of cavernous hæmangioma."

Case 7 : Hæmangioma of Vertebra and of Epidural Space.—A man aged 30 years was first seen by Mr. A. Sutcliffe Kerr in November, 1946. He gave a history of pain in the left knee and weakness of the left lower leg for ten months. The right leg had become weak six months later, and for a month he had noticed some hesitancy of micturition.

EXAMINATION.—He proved to have spasticity of both legs, with extensor plantar responses and a band of hyperæsthesia in the area of the fifth thoracic nerve. *X*-ray examination of the thoracic spine was negative. Lumbar puncture showed no response to Queckenstedt's test. On this occasion the total protein in the cerebrospinal fluid was 70 mg. per 100 c.cm., though three weeks later, when the patient was admitted to Winwick Emergency Hospital, it was only 15 mg. A myelogram, however, showed a complete block between the second and third thoracic vertebræ.

OPERATION.—At operation by Mr. Kerr on Dec. 4, 1946, the spines and laminæ of the first to the third thoracic vertebræ were removed, revealing a localized vascular epidural tumour resembling a secondary deposit. It was dissected away without difficulty.

The pathological report (Dr. M. E. Sharp) on the tumour and on some fragments of the bone overlying it was as follows : " The epidural tumour consists of a mass of fatty tissue richly supplied with capillary blood vessels of varying sizes, and the bone marrow is replaced by similar fatty tissue containing large thin-walled capillaries. The appearances are those of a hæmangioma of the vertebra and of the epidural space."

The patient made an excellent recovery from the operation and was up and about, with normal sphincter control, within three weeks. He subsequently received a course of deep *x*-ray therapy, and remains well without any neurological signs, though he still gets occasional aching pain in his back and a slight sense of instability of the left knee. He is back at work as an upholsterer.

Case 8 : Hæmangioma of the Epidural Space.—A woman aged 45 years was admitted on Sept. 1, 1947, to Walton Hospital, Liverpool, under the care of Mr. A. Sutcliffe Kerr. She gave a history of dull aching pain in the left groin for four years, followed by progressive weakness and numbness of the legs in the last nine months. She had occasionally fallen in the house.

EXAMINATION.—She was found to have spasticity and weakness of both legs, with absent abdominal reflexes and extensor plantar responses. There was hypalgesia and loss of vibration sense below the tenth thoracic dermatome. Lumbar puncture on admission showed 150 mg. of protein per 100 c.cm. and increased globulin but no block to Queckenstedt's test. A fortnight later, however, the paraplegia suddenly became very much more severe. A further lumbar puncture now showed 1,000 mg. of protein per 100 c.cm., and a complete block to Queckenstedt's test. Myelography revealed an arrest of the opaque medium opposite the body of the fourth thoracic vertebra.

OPERATION.—The next day the spines and laminæ of the third to fifth thoracic vertebræ were removed. A grey, soft, vascular tumour surrounded by a thin capsule was discovered on the posterior aspect of the spinal dura. It measured 4 cm. in length and extended into the intervertebral foramina, forming quite a large lateral extension between the fourth and fifth thoracic vertebræ on the left side. The tumour was eventually removed intact.

At the time of writing, four months after her operation, the patient is slowly recovering some power in her legs, but is not yet able to stand or walk unaided.

Discussion

The ætiology of spinal hæmangiomas has been discussed by many of those writers to whom reference has already been made. Some have regarded them as pure congenital anomalies, some as true neoplasms, while a few have even sought to establish the role of trauma or of syphilis in their production. To this question the present communication can give no final answer. One can only suggest that these tumours are, as many writers have suggested of hæmangiomas in general, congenital anomalies, but capable of growth : for the histological appearance of the less mature specimens speaks strongly for their being true neoplasms, while the number of small inert hæmangiomas which may be found among subjects of all age-groups at routine autopsy—in Schmorl's laboratory it was more than 10 per cent. of all spines examined—also strongly suggests a congenital defect. Perhaps the truth is that the hæmangiomas arise in the beginning from a dysplasia of the mesoderm of one or more spinal segments and that thereafter their behaviour is governed largely by the activity of the tissues by which they are surrounded. Thus, as the blood supply of bone decreases once growth is complete, so the intravertebral hæmangiomas are usually well differentiated and inert. But the epidural hæmangiomas, growing in a more active medium, are more prone to partial or total blastomatous transformation. All possible grades of this transformation are recorded in the literature and more than one was found even in the small series presented in this paper.

But not only do these tumours vary in the minutiæ

of their cellular structure. They also show several intermediate stages in situation between the purely vertebral and the purely epidural hæmangiomas. A vertebral tumour may have an epidural extension of greater or less size, an epidural one may be associated with more or less hæmangiomatous change in the vertebræ around it : the only rarity is for the hæmangiomatous process to transgress the barrier of the dura mater.

Possibly an unduly rigid division between the vertebral and purely epidural tumours has sometimes in the past resulted in an imperfect understanding of the pathology of the spinal cord compression to which they may give rise. It is usually stated that cord symptoms may be produced in one of three ways :

1. By collapse of the vertebral body (Deetz, 1901 ; Muthmann, 1903 ; Ewing, 1928 ; Ireland, 1932 ; Boudreaux, 1936 (Fig. 18 (a) and (b)) ; Zdansky, 1936).

2. By expansion of the affected bone causing a diffuse narrowing of the spinal canal without any element of collapse. That this is the commonest cause of cord symptoms is suggested by the work of Schlezinger and Ungar (1939) and of Ghormley and Adson (1941). Several cases which have sometimes been referred to in the past as of " epidural extensions " of vertebral hæmangiomas (Perman, 1926 ; Bailey and Bucy, 1929 ; Roith,[1] 1931 ; Clavelin and Gauthier, 1932) are almost certainly to be placed in this group.

3. By the protrusion of a mass of tissue of varying degrees of hardness from the affected vertebra into the epidural space (Gerhardt, 1895 ; Ribbert, 1912 ; Trommer, 1919-20 ; Gold, 1926 ; G. Guillain and others, 1928 ; Jiano and others, 1931 ; Junghanns, (1932 b) ; Fumarola and Enderle, 1934 ; Boudreaux, 1936 (Obs. 2) ; Clausnizer, 1937 ; Karshner and others, 1939 ; de Gispert Cruz and Tolosa, 1943 ; Shenkin and others, 1945[2]). Almost all these cases betrayed their vertebral origin by containing spicules of bone or by being covered by periosteum. The protrusion sometimes takes the form of a small nodule, and sometimes of a finger-like projection several cm. in length which grows upward or downward in the spinal canal.

But as Elsberg (1941) has pointed out, citing a personal experience, there is a further small group of cases in which a hæmangioma of the spinal epidural space occurred in conjunction with a vertebral hæmangioma and caused symptoms of cord compression. Other examples would appear to have occurred in the cases recorded by Hille (1924), Connell and Hay (1930), Alpers and Pancoast (1932), Boudreaux (1936, Obs. 1), and certainly in the present Cases 4 and 7. Sometimes the degree of bone invasion was found to be slight, as in Connell and Hay's (1930) case, while in other cases the whole vertebra was involved ; but in no instance was there any suggestion that tissue from the affected vertebra itself had been extruded into the epidural space. Rather, the neoplastic process was involving both vertebra and epidural tissue.

Unfortunately from the statistical point of view, cases of vertebral hæmangioma with cord compression are often treated by radiotherapy without biopsy or exploration, so that the exact pathology of the compressing agent remains unverified and therefore the relative frequency of the four types of compression which have been described cannot be accurately assessed.

The clinical signs of the hæmangiomas of the epidural space, whatever their exact point of origin, have been those of progressive paraplegia of varying rapidity of onset, but usually developing within a few months. In Johnston's (1938) case the paraplegia was both sudden and complete and was shown at autopsy to have resulted from a spontaneous epidural hæmorrhage from the vessels of the tumour. Unfortunately this event was not associated either with a complete block to Queckenstedt's test or with a significant elevation of cerebrospinal fluid protein, and laminectomy was therefore not performed. A period of premonitory pain in the back has, as might be expected, occurred more frequently in those cases where the body of the vertebra was involved. Sacral sensory changes and sphincter disturbances were prominent in some cases but totally absent in others ; root pains were similarly inconstant. Cutaneous hæmangiomas were only found in three cases (Devic and Tolot, 1906 ; Johnston, 1938 ; Kaplan, 1942) and pigmented nævi of the skin of the back once (Karshner and others, 1939). Hæmangiomas of the liver and spleen were occasionally found in the cases which came to autopsy. In Devic and Tolot's (1906) case of a purely epidural hæmangioma the cord compression seems to have been due at least in part to an associated intradural but extramedullary tumour which, after some discussion, the authors termed an angiosarcoma. This interpretation of the tumour has been accepted by subsequent writers, but the original description and drawing of the histological preparation suggest very strongly that the intradural neoplasm was in fact a meningioma, though an extradural cavernous hæmangioma was also present.

In two cases in the literature a vertebral hæmangioma was present without being the cause of the spinal cord symptoms of which the patient com-

[1] This case was also recorded from the pathological point of view by Scherer (1933).

[2] The case of a vertebral hæmangioma with epidural " granulation tissue " reported by Hammes (1933) is probably similar.

plained. Saltykow (1909) reported a vertebral hæmangioma with a small epidural extension in a patient dying of advanced tuberculosis involving other vertebræ. He himself believed that the hæmangioma was too small to have caused a paraplegia. In Sandahl's (1931) case a vertebral hæmangioma was a purely incidental finding and the symptoms arose from a " neurinoma " attached to a nerve root, which was successfully removed.

In two cases a previously symptomless epidural hæmangioma has apparently shared in the general venous engorgement of pregnancy and has thus come to cause temporary paraplegia. The first was the case recorded by Balado and Morea (1927), of a woman of 36 who gave a history of paralysis of the legs towards the end of six out of seven pregnancies. On four occasions the symptoms had cleared up immediately after labour, and in the remaining two had lasted respectively one month and five months afterwards. She came under observation at the end of the eighth pregnancy, paraplegia being again far advanced, but she died of heart failure before delivery. At autopsy an epidural angiolipoma was found which extended from the second to the seventh thoracic vertebræ. The second example, the present Case 4, is very similar. Such a history of successive attacks of paraplegia over a period of years with complete remissions between them might in future be regarded as suggestive of an intraspinal hæmangioma. Otherwise the diagnosis is unlikely to be made without operation except where radiological evidence of a hæmangioma of the vertebræ is present or in those very few cases where cutaneous hæmangiomas are found.

From the anatomical and symptomatological point of view the present communication has tended to minimize the difference between the vertebral and the purely epidural hæmangiomas. In respect of treatment, however, the two groups present rather different problems. The purely epidural tumours require exploratory operation, without which the diagnosis can never be made with certainty and cannot always even be suspected. The results vary with the histological nature of the tumour. Of twelve cases of mature hæmangioma submitted to operation (nine in the literature and three in the present series) the tumour was removed in ten, with one postoperative death. Of the cases which survived, one is too recent to assess but the other eight showed a gratifying degree of neurological improvement. There is no report of a recurrence of symptoms in this group. Of the two cases in which the tumour was too vascular to be removed, one was unimproved by operation but one survived twelve years much improved by the decompression afforded.

Of fourteen cases of epidural hæmangioendothelioma and hæmangioblastoma which were submitted to operation two died in the immediate postoperative period. Six of the remainder received no further treatment, of which one was unchanged, three were improved, and two had a recurrence of symptoms within two years.

The remaining six received radiotherapeutic treatment as well, and again one was unchanged, three were improved, and two suffered a recurrence within two years. However, although these figures hardly demonstrate the value of radiotherapy, it should be added that in the group untreated by radiotherapy the recorded period of freedom from recurrence are in all cases less than two years, while in the three treated cases the periods of freedom were five, eight, and eleven years respectively. It would, therefore, seem wise to leave open at present the question of the use of radiotherapy in treating this condition.

In the case of vertebral hæmangiomas with cord symptoms the problem is rather different. A correct diagnosis can usually be made without operation, because of the presence of typical *x*-ray changes in the affected vertebra, and it is well established that, as Nattrass and Ramage (1932) and Ireland (1932) originally showed, radiotherapy can relieve cord symptoms as well as those due to local changes in the bone itself. The long-term results of radiotherapeutic treatment are good. Ferber and Lampe (1942), for example, reported that twelve out of thirteen cases were substantially improved for a period of years, whereas operation has only secured 50 per cent. of neurological recoveries and has carried a mortality of 20 per cent.; though it should be pointed out that many of the recorded cases were operated upon in the days before modern methods of resuscitation were available.

There is one real hazard of radiotherapy, which is illustrated by the experience of Freedman (1940), who recorded a case in which a partial cord lesion due to a vertebral hæmangioma progressed rapidly to completeness during a course of deep *x*-ray treatment. The situation was saved only by immediate laminectomy. One may therefore tentatively suggest that there is still a place for preliminary decompression by laminectomy in cases where paraplegia is far advanced, lest the reaction to radiotherapeutic treatment should cause complete and irrecoverable cord damage. And there is one other occasion on which operation seems to be strongly indicated, and that is when the paraplegia is of sudden onset. For this event has twice (Johnston, 1938 ; Kaplan, 1942) been found to be due to a spontaneous epidural hæmorrhage. But except in these cases—and of course those like the present

Case 4, in which radiological methods have failed to establish the nature of the compressing lesion—the advocates of radiotherapy for vertebral hæmangioma, with or without cord symptoms, seem to have proved its efficacy as the standard method of treatment, while the role of operation is a subsidiary one. The clinician must make an individual judgment on the merits of each case, not forgetting that total extirpation of vertebral hæmangiomas by operation is rarely, if ever practicable.

Summary

1. The literature relating to hæmangiomas of the spinal epidural space, including those which arise from the vertebræ, is surveyed and eight cases are recorded.

2. Comment is made upon ways in which vertebral and epidural hæmangiomas can cause spinal cord compression.

3. The clinical features are discussed, and a rare syndrome of remittent attacks of paraplegia occurring during pregnancy is mentioned as characteristic of an intraspinal hæmangioma.

4. Some points regarding treatment and prognosis are noted.

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References

Alpers, B. J., and Pancoast, H. K. (1932). *Surg. Gynec. Obstet.* **55,** 374.

Antoni, N. (1936). In Bumke-Foerster's "Handbuch der Neurologie." Springer. Berlin. **10,** 70.

Bailey, P., and Bucy, P. C. (1929). *J. Amer. med. Ass.*, **92,** 1748.

Balado, M., and Morea, R. (1927). *Arch. argent. neurol.*, **1,** 345.

Bériel, L. (1922). *Lyon Méd.*, **131,** 777.

Boudreaux, J. (1936). "Les Tumeurs Primitives du Rachi." Vigot Frères. Paris. p. 137.

Bucy, P. C. (1932). *Surg. Clin. N. Amer.*, **12,** 1323.

Clausnizer, H. (1937). *Dtsch. Z. Nervenheilk.* **142,** 276.

Clavelin and Gauthier. (1932). *Rev. Chir., Paris*, **70,** 308.

Connell, W. T., and Hay, W. D. (1930). *Canad. med. Ass. J.*, **22,** 75.

Cornil, L., and Mosinger, H. (1932). *Ann. d' anat. path.*, **9,** 955.

Dandy, W. E. (1925). *Ann. Surg.*, **81,** 223.

De Gispert Cruz, I., and Tolosa, E. (1943). *Rev. Clin. Espaň.*, **9,** 197.

Deetz, E. (1901). *Münch. med. Wschr.*, **48,** 1506.

Devic, E., and Tolot, G. (1906). *Rev. Méd. Paris* **26,** 255.

Dott, N. M. (1947). Personal Communication.

Elsberg, C. A. (1941). "Surgical Diseases of the Spinal Cord." H. K. Lewis. London. p. 331.

Ewing, J. (1928). "Neoplastic Diseases." Third Edit. Saunders. Philadelphia. p. 249.

Ferber, L., and Lampe, I. (1942). *Arch. Neurol. Psychiat. Chicago.* **47,** 19.

Freedman, E. (1940). *Clin. Bull. Western Reserve Univ.*, **4,** 34. Quoted by Ferber and Lampe (1942).

Fumarola, G., and Enderle, C. (1934). *Z. ges. Neurol. Psychiat.*, **150,** 411.

Gerhardt, D. (1895). *Dtsch. Z. Nervenheilk*, **6,** 127.

Ghormley, R. K., and Adson, A. W. (1941). *J. Bone Jt. Surg.*, **23,** 887.

Globus, J. H., and Doshay, L. J. (1929). *Surg. Gynec. Obstet.*, **48,** 345.

Gold, E. (1926). *Arch. klin. Chir.*, **139,** 729.

Grapiolo, A., and Morea, R. (1944). *Prensa méd. argent.* **31,** 319.

Guillain, G., Decourt, J., and Bertrand, I. (1928). *Ann. Méd.*, **23,** 5.

Guillain, P. (1933). Thése de Paris. Quoted by Boudreaux (1936).

Hammes, E. M. (1933). *Arch. Neurol. Psychiat., Chicago*, **29,** 1330.

Hille, K. (1924). *Münch. med. Wschr.*, **71,** 1241.

Ireland, J. (1932). *Amer. J. Roentgen.*, **28,** 372.

Jiano, J., Grigoresco, D., and Vasiliu, D. (1931). *J. Chir., Paris*, **38,** 652.

Johnston, L. M. (1938). *J. Amer. med. Ass.*, **110,** 119.

Junghanns, H. (1932a). *Arch. klin. Chir.*, **169,** 204.

——(1932b). *Ibid.*, **169,** 321.

Kaplan, A. (1935). *J. Mt. Sĩnai Hosp.*, **2,** 64.

——(1942). *Amer. J. Surg.*, **57,** 450.

Karshner, R. G., Rand, C. W., and Reeves, D. L. (1939). *Arch. Surg.*, **39,** 942.

Liebscher, C. (1901). *Prag. med. Wschr.*, **26,** 189.

López Ibor, J. J., and Peraita, M. (1941). *Actas Espaň. Neurol. Psiquiat.*, **2,** 93.

Mixter, W. J. (1932). Dean Lewis's "Practice of Surgery," **12,** 54.

Muthmann, A. (1903). *Virchows Arch. path. Anat.*, **172,** 324.

Naffziger, H. C., and Brown, H. A. (1933). *Arch. Neurol. Psychiat., Chicago.* **29,** 561.

Nattrass, F. J., and Ramage, D. (1932). *J. Neurol. Psychopath.*, **12,** 231.

Perman, E. (1926). *Acta. chir. scand.*, **61,** 91.

Petit-Dutaillis, D., and Christophe, J. (1931). *Rev. Neurol.*, **2,** 824.

Rand, C. W. (1927). *Arch. Neurol. Psychiat., Chicago.*, **18,** 755.

Rasmussen, T. B., Kernohan, J. W., and Adson, A. W. (1940). *Ann. Surg.*, **111,** 513.

Ribbert, H. (1912). *Dtsch. med. Wschr.*, **38,** 390.

Roith, O. (1931), *Zbl. Chir.*, **58,** 3028.

Saltykow, S. (1909). *Verhandl. deutsch. Path. Gesellsch. Leipzig.* p. 370.

Sandahl, C. (1931). *Acta chir. scand.*, **69**, 63.
Scherer, E. (1933). *Beitr. path. Anat. allg. Path.*, **90**, 521.
Schlezinger, N. S., and Ungar, H. (1939). *Amer. J. Roentgen.*, **42**, 192.
Shenkin, H. A., Horn, R. C., and Grant, F. C. (1945). *Arch. Surg.*, **51**, 125.
Trommer, B. (1919-20). *Frankf. Zr. Path.*, **22**, 313.
Turner, O. A., and Kernohan, J. W. (1941). *Arch. Neurol. Psychiat., Chicago*, **46**, 444.
Wyburn-Mason, R. (1943). "The Vascular Abnormalities and Tumours of the Spinal Cord and its Membranes." Henry Kimpton. London. *Passim.*
Zdansky, E. (1936). *Fortsch. Geb. Röntgenstrahlen*, **54**, 263.

THE LAMINAR PATTERN OF THE LATERAL GENICULATE BODY IN THE PRIMATES

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In the past the lateral geniculate body has tended to receive less than its due share of attention in the investigation of the neural basis of vision. Yet a detailed study of the intermediate cell station in the lateral geniculate body is clearly an essential part of such an investigation. The anatomical situation of the nucleus renders it difficult of direct experimental approach, and our present knowledge of it still rests largely on elementary anatomical methods.

The stratified structure of the lateral geniculate body is well known, and in the higher Primates it may consist of as many as six laminæ. The termination of crossed and uncrossed optic nerve fibres in alternate laminæ is also well established. Brouwer and Zeeman (1925, 1926) worked out a gross quadrantic projection of the retina in the nucleus by the application of the Marchi technique, and the details of this projection were further elucidated by Le Gros Clark and Penman (1934) by the study of transneuronal degeneration following small localized retinal lesions. Little, however, is yet known of the significance of the laminar disposition in different parts of the nucleus. Some misunderstanding in the past regarding the form and folding of the geniculate laminæ has evidently resulted from the difficulty of interpreting individual sections cut in different planes. For instance, in the human lateral geniculate body, a section in one plane gives the appearance of " inversion " of the laminæ, with the large cell laminæ forming the outermost layer, in another plane a pattern of " eversion " may be seen, and in a third plane both eversion and inversion become evident. So, also, the number of laminæ may appear to vary according to the plane in which the section is taken. Hence it becomes necessary to make reconstruction models so that the intranuclear differentiation and disposition of all the layers can be easily visualized. Thuma (1928) adopted this method in his study of cat's lateral geniculate body, as also did Balado and Franke (1937) in their comprehensive work on the human geniculate body. Le Gros Clark did the same for *Macaca mulatta* (1941). This method further clarifies the relation of the nucleus to the surrounding neural structures, and facilitates the mapping of the projection fields of the retina. The significance of changes in the laminar pattern in a phylogenetic series can also be studied. Above all it affords an opportunity for a comparative study of the anatomical basis of the binocular and monocular representation fields, the central and peripheral vision fields, and changes in the lateral geniculate body associated with incomplete or hemi-decussation of optic nerve fibres.

Materials and Methods

Wax reconstruction models were made of the lateral geniculate body of Man, *Lemur fulvus* (brown lemur), and *Microcebus murinus* (mouse lemur). In the case of the human brain, a block of tissue containing the right lateral geniculate body was embedded in paraffin, and serial sections (10 μ in thickness) were cut transversely to the axis of the optic tract. The sections were stained with Borell's methylene blue. The outline of the nucleus and its laminæ in every fifth section (out of a total of 835) was traced with a projection apparatus at a magnification of 30 diameters and a model reconstructed by the blotting-paper and beeswax method. Serial sections of the lateral geniculate body of the brown lemur were cut (15 μ) in the long axis of the optic tract (which ascends to reach the lower end of the body and spreads over its outer surface). Tracings of every third section (out of a total of 300) were made at a magnification of 50 diameters. The same procedure was repeated on serial coronal sections (15 μ) of the lateral geniculate body of *Microcebus murinus*, cut in the long axis of the optic tract; tracings of every other section (out of a total of 186) under a magnification of 50 diameters were made for the reconstruction of the model.

I am indebted to Professor Le Gros Clark for the reconstruction model of the geniculate nucleus of *Macaca mulatta* and the serial sections used for preparing the model, as well as for other material prepared by him during his previous work on the subject.

In order to facilitate the observations on the intranuclear laminar pattern after the models were completed, and also the task of their description, they were mounted in detachable blocks the boundaries of which were located approximately at points of maximum change in internal pattern at different levels. This type of construction permits an examination of the way in which a particular internal pattern in one local region passes into a different pattern in the adjacent region. The model of the human lateral geniculate body was mounted in seven blocks. The " pregeniculate " body, which is not in structural continuity with the main nucleus, was fixed in its correct position in relation to the most rostral section by a strip of metal plate. The model of the lateral geniculate body of *Lemur fulvus* was mounted in four blocks and that of *Microcebus* in two. In order to estimate the relative positions and proportions of large-celled and small-celled elements on the models, the areas of distribution of these two elements were painted in two different colours.

Descriptive Observations

Human Lateral Geniculate Body.—The form of the lateral geniculate body in Man was first described in 1905 by von Monakow. According to him it consists of the main part (*Haupt-teil* or *Teil des Hilus*), a lateral horn (*Sporn Anteil*), and an anterior part where the fibres of the optic tract enter the nucleus (*Retina Anteil*). In 1918 Winkler described it as consisting of the *Kopf des Ganglion* or the *caput* and the *Sporn* or *cauda*. In 1937 Balado and Franke described the form of the lateral geniculate body with the help of a reconstruction model. They described it as having an oval form, the long axis of which runs from before backwards, but they pointed out that their description did not tally with the classical description of Monakow and Winkler. It is, however, difficult to understand the illustrations they give of their model, for the latter shows very little correspondence with the well-recognized shape and proportions of the human geniculate body.

The form of the human lateral geniculate body as demonstrated by our model may be briefly described as follows (see Figs. 2, 3, and 4). It consists of: (1) a thick, prominent main part with a shallow " hilum " ventrally and a dorsal convexity rising to a prominent antero-posterior crest, and (2) a lateral flange-like extension, or lateral horn, curving laterally with its lateral free margin tipped upwards. The small rounded eminence seen in the course of the optic tract in the gross dissection of the base of the brain, which in descriptive anatomy is usually designated as the " lateral geniculate body," is really the ventral convex surface of the lateral horn.

There is no symmetry of form on either side of the dorsal crest. Laterally, the dorsal surface of the main part slopes down abruptly to an irregular sulcus which marks it off from the lateral horn. Medial to the crest the dorsal surface presents different features at different levels. The anterior third of this surface is extremely uneven, the laminæ being here broken up into irregular projections by the sweeping entrance of the optic tract fibres. Some of the irregularities are so prominent that Balado and Franke have described them as special " *Spornen*." This region corresponds to the " *Retina Anteil* " of Monakow. In the middle third the dorsal surface slopes very gradually from the dorsal crest to terminate medially in an incurved blunt rounded " medial tubercle." In the posterior third the medial surface slopes abruptly from the crest and continues into the posterior end of the concavity on the ventral surface of the nucleus. The medial margin of the nucleus is marked by the free edges of some of the constituent laminæ separated from one another by grooves. The main dimensions of the lateral geniculate body from which the model was constructed were as follows: Antero-posterior diameter (excluding the pregeniculate nucleus) 8·35 mm., maximum breadth 5·0 mm., maximum height 4·5 mm.

In summary, the nucleus is a concavo-convex body with the dorsal surface convex medially and concave laterally, and the ventral surface correspondingly concave medially and convex laterally. This is related to the fact that, as can readily be seen in Fig. 3, in the main part of the nucleus medially the constituent laminæ are curved with a ventral concavity (everted), while laterally, in the lateral horn, they are convex ventrally (inverted). The salient surface features are: (1) the dorsal crest with its prominent, rounded posterior end marked by curving ridges and grooves; (2) the medial tubercle; (3) the rostral irregular part in relation to the entering optic tract; and (4) the lateral horn.

A small elongated cellular mass, usually known as the corpus pregeniculatum, appears within the lateral division of the optic tract before the oral pole of the main part of the lateral geniculate body makes its appearance in transverse sections. However, a number of specimens need to be studied before a definite conclusion is to be arrived at regarding the nature of this mass and its relation to the main nucleus. The cells are of the same type as those of the lateral geniculate body proper. The more ventrally situated cells are larger and more deeply stained than the others.

Laminar Organization.—The layers of the lateral geniculate body have been variously named by different investigators, but in this communication they will be referred to as layers 1, 2, 3, 4, 5, and 6,

of which the ventral two large-celled layers are layers 1 and 2 and the four small-celled layers are 3, 4, 5, and 6 from below upwards. The number of laminæ and their arrangement will be mentioned in the order of their appearance in serial sections from before backwards (see Fig. 1).

Half a millimetre from the oral pole layers 1 and 4 first become recognizable as two distinct layers, layer 1 as a thin, ventral, large-celled layer, and layer 4 as a thicker, dorsal, small-celled layer (Fig. 1a). A quarter of a millimetre further caudally, the layers 1, 4, and 5 become distinct (Fig. 1b). At a distance of 2·5 mm. from the oral pole, the following laminar pattern is present: the layer 6 has now appeared and is seen arching over layer 5, layers 4, 5, and 6 are not differentiated from each other at their lateral ends and layer 3 appears below and close to layer 4 (Fig. 1e). There is an irregular distribution of large cells near the ventral border of layer 3, while layer 1 shows its maximum ventral concavity at this level. Three millimetres from the oral pole all the six layers of the geniculate body are well defined. Layer 1 becomes more horizontal, and layer 2, though distinct, is not at this level separated from the layer 3 by a medullary lamina. Layers 3, 4, 5, and 6 are distinct and separated from one another by medullary laminæ (Fig. 1g, h). Layers 4 and 6 unite at the medial and lateral extremities of the layer 5 and continue into the medial tubercle and lateral spur as a fused layer. At more caudal levels all six layers become well defined in the main segment of the nucleus, with interweaving medullary laminæ separating them. Composite laminæ formed by the fusion of layers 4 and 6 and of layers 3 and 5, together with separate layers 2 and 1, extend into the medial tubercle and lateral horn to constitute those parts of the geniculate body. In other words, these parts are typically composed of four laminæ only, 1, 2, 3+5, and 4+6. Near the caudal pole (in sections taken transversely to the axis of the optic tract) the medial tubercle is absent, the six layers occupy the main part of the nucleus and appear relatively diminished in size, and in this region the laminar structure also becomes more complex. On the other hand the lateral horn maintains its four-layered character more or less throughout the antero-posterior extent of the geniculate body.

Numerical Data.—In order to determine the total number of cells in the lateral geniculate body and their distribution between the crossed and uncrossed laminæ and between large- and small-celled elements, the following procedure was adopted. The outlines of layer 1, layer 2, layers 4+6, and layers 3+5 were traced with a projection apparatus at a magnification of 30 diameters. This was done in every fifth section in the first 20 sections, every tenth section in the next 120 sections, every twentieth section in the next 620 sections, and every fifth section in the last 80 sections. The areas enclosed by the outlines of the above laminæ were measured with a planimeter. By the numerical integration of the planimeter measurements, the following volumes were estimated:

Layer 1	0·0054 c.cm.
Layer 2	0·0031 c.cm.
Layer 4+6	0·0289 c.cm.
Layer 3+5	0·0232 c.cm.

Total volume of large-celled layers ..	0·0085 c.cm.
,, ,, ,, small-celled layers ..	0·0521 c.cm.
,, ,, ,, crossed layers	0·0343 c.cm.
,, ,, ,, uncrossed layers ..	0·0263 c.cm.
,, ,, ,, all layers	0·0606 c.cm.

Next, the density of cells in the various layers was determined. The mean number of cells was estimated by counting the cells in 15 areas of 0·05 sq. mm. taken at random in each layer. The thickness of the sections was 10 μ, and the cell density was calculated in millions per c.cm. The results are as follows:

	Density (millions per c.cm.)	
	Crossed	Uncrossed
Large cells	14·1 ..	11·6
Small cells		
Section no. 10–135 ..	14·2 ..	12·1
,, ,, 155–375 ..	19·8 ..	19·2
,, ,, 395–755 ..	22·9 ..	22·1
,, ,, 760–815 ..	6·5 ..	5·8

The total number of cells was estimated by multiplying the densities by the volumes of corresponding portions of the geniculate body. The results are:

	Total cells in thousands		
	Large cells	Small cells	Total
Crossed layers ..	75±2·4	612±9·6	687±10·0
Uncrossed layers ..	36±1·9	487±9·3	523± 9·5
Total	111±3·1	1099±13·4	1210±13·7

The ratio between the volume of crossed and uncrossed layers is 34 : 26. The density of the cells is greater in crossed than in uncrossed layers, and the cell ratio between these two sets of layers is 56 : 43.

The number of large cells is about one-tenth that of the small cells, and it may be noted that the figures of Balado and Franke for Man show a proportion of between one-fifth and one-sixth, and those of Le Gros Clark for *Macaca* one-seventh to one-eighth.

The total number of small cells according to our estimate is of the order of 1,100,000 and that of the large cells 110,000, together making a total of about 1,210,000. Balado and Franke (1937) give an estimate of 482,664 of small cells and 86,181 large cells with a total of 568,845. It is difficult to explain the discrepancy as the method which they used for their computation is not known. Taking into account the earlier estimates of the number of fibres in the human optic nerve (Zwanenburg, 440,000;

Kappers, 550,000; and Krause, 400,000), they conclude that the number of cells corresponds to the number of optic fibres terminating in the geniculate body and that a 1 : 1 cell-fibre ratio, therefore, exists. A later computation by Bruesch and Arey (1940) shows that the number of optic fibres may vary from 564,776 to 1,140,030. Arey and Bickel (1935) reported an average of 1,270,000 fibres in six optic nerves taken from individuals between 1 and 57 years of age. It may be mentioned that Krause's (1876) earlier estimate was 1,000,000 and his second estimate, quoted by Balado and Franke, was really an estimate of the large or thick fibres. However, it may be noted that the range of variation in the estimates of the number of optic nerve fibres by the various observers appears to correspond with the range of variation in the estimates of the cell content of the geniculate body, as shown by our results and those of Balado and Franke. If the fibre-cell ratio is constant, an average of a 1 : 1 ratio may still hold good even for the extreme values.

Glees and Le Gros Clark (1941) reported that in the monkey the optic nerve fibres divide into 5 or 6 branches in the small-celled laminæ, implying a 1 : 5 or 6 ratio in those regions. If the 1 : 1 ratio applies to the geniculate body as a whole of this animal, then their further observation that no branching is seen in large-celled layers is significant and would mean a convergence of more than one optic fibre to a single large cell. In this connexion it may be mentioned that the 5 or 6 terminal branches were probably observed by these authors in the central vision area, and it is possible that the number of branches may be different in the peripheral vision area. It may also vary in the different laminæ.

The total laminar volume of the human geniculate body is estimated to be 60·6 c.mm. The ratio of the volume of all the " crossed " layers to that of all the " uncrossed " layers is 343 : 263. On the other hand, the density of cells is slightly greater in the " crossed " laminæ. The ratio of the number of cells of the " crossed " large-celled layer to that of the " uncrossed " large-celled layer is 2 : 1, that for the small-cell layers being 5 : 4. The ratio of the total number of cells in both the " crossed " and " uncrossed " laminæ in the whole nucleus is 56 : 43 (or approximately 3 : 2). If the fibre-cell ratio is constant for adjacent " crossed " and " uncrossed " laminæ, then this ratio would also apply to the crossed and uncrossed fibres of the optic tract terminating in the geniculate body. Previous estimates of the ratio of crossed and uncrossed fibres of the optic tract in man are those of Cajal (1899), 2 : 1, and Sántha (1932), 3 : 2. In *Macaca*, Le Gros Clark found the ratio to be 3 : 2.

The Projection of the Retina on the Human Lateral Geniculate Body

Experiments on monkeys have served to establish the general principle of a " point to point " projection of the retina on the lateral geniculate body in the higher Primates. The phrase " point to point " needs some modification in this connexion, as will be discussed below, but its general meaning is no doubt acceptable.

For the purpose of mapping the retinal projection areas in our reconstruction model of the human geniculate body, the available data based on experimental studies on the monkey's brain are not altogether applicable, for the details of the laminar pattern in Man and monkey are not entirely comparable. Recourse has therefore been had to reports on clinical cases of partial defects in the field of vision associated with localized secondary degeneration in the geniculate body. Unfortunately, detailed accounts of the extent and distribution of geniculate cell atrophy in such cases are relatively few, but those that are available provide important information. Rönne (1910, 1913) reported four cases of alcoholic amblyopia and two of diabetic amblyopia in which degeneration of the papillomacular bundle (with a central scotoma) was associated with localized areas of transneuronal degeneration in the geniculate body. His description of the extent of the localized geniculate atrophy is amplified by good microphotographs and excellent diagrams. In 1930, Brouwer reported a case of hemianopia with macular sparing to the extent of 12° in the horizontal and 20° in the vertical meridian (in a normal field, according to Traquair, the macular area of the retina covers a visual angle of 15° to 20°). The evidence provided by the secondary degeneration in the geniculate body is complementary to that derived from Rönne's cases of amblyopia.* In 1914, Rönne reported a case of left-sided hemianopia in which macular sparing was not noticeable by perimetric tests but was just evident on a Bjerrum screen. The extent of the spared macular area amounted to about 1° at the fixation point. In this critical case, thionin preparations of the right geniculate body showed severe cell degeneration, but normal cells were found in a small localized region in the caudal 2 mm. of the nucleus (at which transverse level the degeneration affected only the lateral horn or " cauda "). The importance of this case is the evidence which it provides for the localization of the foveal centre in the lateral geniculate

* The writer has to thank Professor Brouwer for the opportunity of making a personal examination of the sections of the geniculate body from his case of hemianopia. A glass plate reconstruction was made in order to define accurately the extent of the degenerated area, and this proved to be particularly useful for locating the boundaries of the central and peripheral projection areas in the wax reconstruction model.

body. In 1912, Winkler published the results of an anatomical study of two relevant cases of a mutually complementary nature. The first was a right lower homonymous hemianopia with the macula wholly affected in the right visual field and partly affected in the left. The other case was an upper homonymous hemianopia. A further case of a lower homonymous hemianopia was described by Polyak in 1942.

By reference to the basic data derived from the anatomical descriptions and diagrams in these clinical reports, it has been possible to plot the distribution and extent of the retinal projection areas in our reconstruction model in considerable detail (see Fig. 4). The main results of this study are as follows. The whole of the lateral horn of the lateral geniculate body constitutes the projection area for the lower peripheral quadrant of the retina, and it is interesting to note that, on the reconstruction model, a fairly distinct sulcus on the dorsal aspect of the geniculate body, and a less conspicuous groove on its ventral aspect, serve to mark externally the junction of the representation of the peripheral field of vision with that of the central field. The somewhat uneven region of the rostral third of the nucleus, together with the medial tubercle with which it is in continuity, comprises the whole projection area for the upper peripheral quadrant of the retina. The so-called " small inner segment " which is usually referred to, in transverse sections of the nucleus, as representing the upper peripheral quadrant is, in fact, only that part of this area comprised by the medial tubercle. On the ventral surface of the geniculate body the upper peripheral quadrant is demarcated from the central projection area by a groove, but on the dorsal aspect this functional boundary is not indicated by any external marking. The projection area for central vision has the form of an inverted pyramid with a convex base forming the arched elevation or crest on the dorsal aspect of the geniculate body, and a flattened apex ventrally. It is covered in front and over the rostral half of its medial aspect by the area for the upper peripheral visual field, and its lateral margin is related throughout its antero-posterior extent to the lower peripheral field area. The central projection area of the geniculate body is everywhere composed of six separate cell laminæ, the ventral large-celled layers 1 and 2, and the dorsal small-celled layers 3, 4, 5, and 6. Of these layers, as is now well established, 1, 4, and 6 receive crossed retinal fibres, and 2, 3, and 5 uncrossed fibres. In relation to the inverted pyramidal shape of the central visual field area, the relative extent of the several layers increases from the ventral to the dorsal aspect of the nucleus. Thus, the more dorsally situated layers are the more extensive, while the ventrally placed large-cell layers make a relatively small contribution to the area. Moreover, this contribution of the large-cell layers diminishes progressively towards the region representing the fixation point. In other words, there is a great preponderance of the small-celled elements of the geniculate body in the area for central vision.

In general, the peripheral visual segments of the geniculate body present only four cell laminæ, the two large-celled layers 1 and 2, and two small-celled layers formed by the fusion of layers 3 and 5, and layers 4 and 6. Moreover, in these segments there is a relatively greater preponderance of the large-celled elements than in the area for central vision. The laminar pattern in the projection area for upper peripheral vision, it should be noted, is not so uniform or regular as it is in the area for lower peripheral vision. This is at least partly due to the fact that the laminar arrangement is disrupted and disturbed by the entering fibres of the optic tract, but it remains possible that it may also be related to some functional difference.

If the geniculate body is viewed as a whole, it will be seen that a median antero-posterior section passing through the summit of the dorsal crest and the concavity of the ventral hilum divides the nucleus into halves which are asymmetrical in form but approximately equal in volume. The plane of such a section is the axial plane of the nucleus and represents the horizontal meridian of the retina; the rounded margin of the nucleus at the caudal end of the plane marks the site of projection of the foveal centre or fixation point, while the anterior end of the section represents the far peripheral point along the horizontal meridian of the retina. The posterior two-thirds of the dorsal crest of the geniculate body extends through the central visual field area, while its anterior third marks the boundary between the upper and lower peripheral visual field areas on either side. The vertical meridian of the retina is represented in the geniculate body by its irregular posterior border, extending from the caudal margin of the lateral horn to the back of the medial tubercle. On the other hand, the extreme peripheral margin of the sensitive retina corresponds to the irregular anterior margin of the nucleus.

From the foregoing description, it will be apparent that almost the whole of the human lateral geniculate body is concerned with binocular vision and contains an equal number of " crossed " and " uncrossed " cell laminæ. There is, however, a very small monocular area, represented by a narrow strip extending along the anterior margin of the nucleus (that part which corresponds to the extreme peripheral margin of the sensitive retina). This strip is

distinguished in its intrinsic structure by the exclusion of " uncrossed " laminæ. It is composed only of two " crossed " laminæ, the large-celled layer 1, and a layer formed by the fusion anteriorly of the small-celled layers 4 and 6. These two " crossed " laminæ lose their identity to some extent and merge with each other at the extreme anterior margin of the nucleus.

It was mentioned above that the phrase " point to point," as used to describe the mode of projection of the retina on the lateral geniculate body, needs some qualification. In fact, each " point " in the retina appears to be projected on to a wedge-shaped sector of the nucleus, extending through its whole dorso-ventral thickness and composed of several cell laminæ. The nearer the retinal " point " is to the periphery of the retina, the shorter is the corresponding projection " wedge " in the geniculate body. Similarly, the meridians of the retina are represented in the nucleus not by lines, but by two-dimensional planes of section. It is thus clear that, though the question of the fine and precise representation of the retina in the geniculate body was answered by the experiments of Le Gros Clark and Penman (1934) in a manner favourable to the concept of Henschen (1924), Willbrand (1897), and others, their phrase " point to point " must be taken to mean that each minute locus in the retina is actually projected on to a small circumscribed sector of definite dimensions in the geniculate body. If one could speak of a " visual unit " in the lateral geniculate body, it would be a pyramidal-shaped unit, to be compared with the parallelopipedon (Solnitzky and Harman, 1946) in the visual cortex.

The Lateral Geniculate Body in Lower Primates

Microcebus Murinus (Fig. 5).—A brief account of this nucleus has been previously given by Le Gros Clark (1931) in his study of the brain of *Microcebus*. Our reconstruction model shows that it is a somewhat lentiform body with a maximum vertical diameter of 2·7 mm., a maximum width of 1·1 mm., and an antero-posterior diameter of 2·79 mm. The main mass of the body is prolonged forwards laterally into a prominent lip and converges behind to form a blunt posterior pole. The rostral lip forms the lateral boundary of a concavity which excavates the anterior surface of the nucleus as a whole. This deep concavity is occupied by the emerging fibres of the optic radiation. The medial aspect of the nucleus is separated by a low antero-posterior ridge into dorso-medial and ventro-medial surfaces, of which the former is in relation to the pulvinar and the latter to the medial geniculate body.

In its middle third, the geniculate body is composed of six fairly well defined cell laminæ. The two most superficial laminæ (1 and 2) are composed of large cells, and the remainder of small cells. The deeper laminæ (particularly lamina 6) are composed of densely packed cells and at their ventral ends show a tendency to crinkle into convolutions and to become slightly everted. If the sections are traced rostro-caudally, the small-celled layers increase gradually in number till all the layers become well defined in the middle third (see Fig. 5). More caudally they gradually disappear in a regular order from lamina 6 outwards. The laminæ are dorso-ventrally disposed with a lateral convexity and a medial concavity and thus show the typical lemuroid inversion pattern (Le Gros Clark, 1932).

The relative proportion of the large- and small-celled elements appears to vary with the differentiation of small-celled elements in different transverse planes of the geniculate body. In the middle third, the small-celled elements predominate, and in the caudal third the large-celled elements. The large-celled layers extend over the whole of the convex lateral surface and also curve round the ventral border of the nucleus to reach the ventro-medial surface. They enter into the formation of the latter to an increasing extent towards the caudal end.

No data based on experimental work are available for locating projection areas in lemurs. From the nature of the laminar organization of the monocular and binocular fields in the human geniculate body, the rostral thinner part of the nucleus in *Microcebus* may be considered as the monocular area where the uncrossed laminæ are excluded. The main massive part forms the binocular area. From a comparative study of the projection areas in higher primates and lower mammals as worked out experimentally by Brouwer and others, it is possible to infer that the upper part of the nucleus is the projection field of the lower quadrant of the retina and vice versa.

Lemur Fulvus (Figs. 6 and 7).—The geniculate body of this lemur was included in a previous study by Woollard and Beattie (1927), but their description of it is short and incomplete. Our reconstruction model shows that it is a somewhat irregularly shaped structure, in which the maximum sagittal diameter and maximum width are both about 4·5 mm. Its laminar pattern bears a general resemblance to that of *Microcebus*, but the laminæ are more elaborately folded. The constituent laminæ (as seen in transverse sections) present the inversion pattern, that is to say, they are curved in such a way that the deeper small-celled laminæ are contained within the concavity formed by the superficial large-celled laminæ. The latter are curved in conformity with the convex surface of the thalamus. In the main part of the nucleus, however, the laminæ in the

ventro-medial third become bent in the opposite direction so that here they appear everted. In other words, the laminar pattern in *Lemur fulvus* shows a combination of inversion and eversion, with a predominance of the former. There are four well-defined cell laminæ in this species, which comparative studies indicate are equivalent to laminæ 1, 2, 3, and 6 of *Microcebus* and other lemurs. But there is a relatively large space between laminæ 3 and 6 containing medium-sized and rather faintly staining cells scattered in diffuse formation. This indistinct mass of cells reaches its maximum cross-sectional area in the middle third of the geniculate body and here shows a tendency to split into two ill-defined layers which evidently represent the cell laminæ 4 and 5 found in other lemurs. Thus, although only four laminæ are attributed to *Lemur fulvus* by Woollard and Beattie (1927), a total of six are potentially present. In the rostral half of the nucleus the small-celled elements preponderate, but in transverse sections through the caudal half the large-celled elements occupy a relatively greater area. As in *Microcebus*, the geniculate body of *Lemur* shows a general preponderance of the large-celled elements as compared with the higher Primates.

Macaca Mulatta (Fig. 8).—The reconstruction model of the macaque geniculate body has already been described by Le Gros Clark (1941). Its general appearance is well shown in Fig. 8, where the model is represented from its posterior aspect, cut horizontally through the middle, and the upper and lower halves separated from each other. The nucleus is somewhat pyramidal in shape, with a medially inclined apex above, and a hollowed-out base below. The basal concavity is continued upwards on to the postero-medial aspect of the body to form the "hilum," the sides of which are made up of the everted superficial large-celled lamina (lamina 1). The axis of the folding which forms the hilum corresponds to the junction of the four-layered anterior part of the geniculate body, and the six-layered posterior part. These two parts, as demonstrated by the experimental work of Le Gros Clark and Penman, represent the peripheral and central fields of the retina respectively. Compared with the human and lemuroid types of nucleus, that of *Macaca* presents a completely everted pattern and also shows a somewhat different orientation with respect to the optic tract. The central vision area, which in the human geniculate body is situated posteriorly, in the monkey occupies rather the postero-superior region of the nucleus. Similarly, the monocular area, which in Man forms the rostral margin of the nucleus, is found at the ventral margin. The complete eversion and the apparent rotation of the geniculate body in the monkey is probably related to the pressure of adjacent parts of the brain during development.

Factors which Determine the Form and Position of the Lateral Geniculate Body in the Primates

The relative position of the lateral geniculate body is determined largely by the growth and expansion of neighbouring elements of the thalamus. In primitive mammals, such as insectivores, the nucleus stretches throughout the antero-posterior extent of the lateral wall of the thalamus. With the expansion of the lateral nucleus of the thalamus it becomes first pushed caudally, and then displaced laterally and ventrally. With the ventral displacement there occurs a rotation of the geniculate body, so that the original dorsal and ventral poles become the lateral and ventral margins. These changes in position, with rotation, are to be observed in the Primate series. They account for the fact that, while in lower mammals the projection fields for upper and lower halves of the retina are represented in a reversed form in the lower and upper halves of the geniculate body, in the higher Primates they are represented respectively in the medial and lateral halves of the nucleus.

Intrinsic or functional factors and extrinsic or mechanical factors combine to explain the shape and laminar folding of the geniculate body. In the ascending series of Primates the functional factors are manifested, in the first place, by a relative increase in size of that region of the nucleus which is concerned with binocular vision. This region is proportionately thicker than the monocular region, for the latter, besides being less differentiated in its cellular architecture, includes "crossed" laminæ only. The introduction of a central vision area in the middle of the binocular region is the second functional factor. In the Primate series there is a progressive increase in the total number of small ganglion cells in the retina and especially their concentration in the central area of the retina, and this is correlated with a corresponding elaboration and expansion of the small-celled elements of the geniculate body. It is as a result of this expansion that the small-celled laminæ begin to extend beyond the limitations of the space which, in the inverted type of nucleus, is provided within the concavity of the large-celled elements, and assume a curve in the opposite direction so as to form a local eversion pattern. Although the lower Primates have no differentiated *fovea centralis*, a definite central vision area of the geniculate body is foreshadowed in the genus *Microcebus*, for even in this primitive Primate the deeper small-celled laminæ show a tendency to

expand at their ventral end and to become everted. In *Lemur* this tendency becomes much more pronounced, and in the ventral third of the geniculate body of this genus the cell laminæ undergo a marked local eversion (in contrast to the inversion pattern of the rest of the nucleus). In Man the primitive inversion pattern is still retained in its original form as the lateral horn of the lateral geniculate body, which, as already noted, is concerned with peripheral vision. On the other hand, in the highly elaborated central vision area the laminæ are everted, forming a ventral concavity or " hilum " where branches of the anterior choroidal and posterior cerebral arteries form a particularly rich anastomosis before penetrating into the substance of the nucleus (Abbie, 1933 ; Balado and Franke, 1937). In the monkeys (both platyrrhine and catarrhine) the laminar pattern is entirely of the eversion type, that is, the superficial large-celled laminæ are throughout their extent contained within the concavity of the deeper small-celled laminæ. The hilum of the geniculate body in these groups of Primates is directed ventrally at its rostral end and postero-medially in the rest of the nucleus. As already noted, the completeness of the laminar eversion in the monkeys is no doubt partly due to the expansion of the central vision area of the small-celled elements, but it is evidently also conditioned by mechanical factors, for example, the pressure of adjacent parts of the brain in relation to the proportionately large size of the nucleus itself.

The regional variations in the laminar pattern of the geniculate body in Primates are determined initially by an increase in the relative proportion of uncrossed fibres in the optic tract, which leads to the progressive differentiation of " uncrossed " cell laminæ in the central vision area. In the monocular area of the higher Primates two cell laminæ are usually found, both related to the contralateral eye ; in the rest of the area for peripheral vision there are two sets of two laminæ, the two sets being related to the two eyes ; and in the central vision area there are also two sets, but here, in general, each consists of three laminæ. In the lower Primates the laminar pattern is somewhat variable, and it is not by any means certain that the small-celled layers in the lemuroid geniculate body can be homologized severally with those found in the Anthropoidea. In the New World monkeys, the lamination of the small-celled elements may be indistinct, and in some cases (as in the marmoset) each set consists of two layers only.

The differentiation of magnocellular and parvicellular types of laminæ appears to be characteristic of all the Primates, with the single exception of *Tarsius*, in which all the layers of the geniculate body are composed of cells of approximately similar size. In the higher Primates, the large-celled layers are relatively reduced in the central-vision area of the geniculate body (probably because they are related to the rod rather than the cone elements of the retina). In the lemurs, the large-celled elements show no such regional distribution —they are equally obtrusive over all fields of the geniculate body.

Summary

1. Wax reconstruction models of the lateral geniculate body of Man, *Macaca*, *Lemur*, and *Microcebus* have been prepared and, on the basis of these, the laminar pattern described in each form.

2. The variations of the laminar pattern in relation to monocular, peripheral, and central fields of the retina have been defined.

3. Numerical data regarding the volume and cell content of the different laminæ in the human geniculate body have been obtained, from which it is estimated that in Man the relation of crossed to uncrossed fibres in the optic tract is approximately 3 : 2.

4. The factors determining the form and position of the lateral geniculate body in the Primates have been discussed.

I gratefully acknowledge the active help given by Professor Le Gros Clark in the preparation of this paper. I am indebted to him for suggesting the line of research, for providing the facilities, and for supervising the study. I wish also to thank Mr. D. J. Finney for assistance with the numerical computations, and Miss M. F. Collinson for preparation of the illustrations.

References

Abbie, A. A. (1933). *J. Anat., Lond.*, **67**, 491.
Arey, L. B., and Bickel, W. H., (1935). *Anat. Rec.*, **61**, (Suppl.), 3. (Quoted by Bruesch and Arey.)
Balado, M., and Franke, E. (1937). " Das Corpus Geniculatum Externum." J. Springer. Berlin.
Brouwer, B. (1930). *J. Psychol. Neurol., Lpz.*, **40**, 147.
——, and Zeeman, W. P. C. (1925). *J. Neurol. Psychopathol.*, **6**, 1.
——, ——(1926). *Brain*, **49**, 1.
Bruesch, S. L., and Arey, L. B. (1940). *J. Comp. Neurol.*, 631.
Cajal, S. R. (1899). " Die Struktur des Chiasma Opticum." Leipzig. (Quoted by Rogalsky.)
Clark, W. E. Le Gros (1931). *Proc. Zool. Soc. London*, **30**, 413.
——(1932). *Brit. J. Ophthal.*, **16**, 264.
——(1941). *J. Anat., Lond.*, **75**, 419.
——(1942). *Trans. ophth. Soc. U.K.*, **62**, 229.
——, and Penman, G. (1934). *Proc. roy. Soc.*, B, **114**, 229.
Glees, P., and Clark, W. E. Le Gros (1941). *J. Anat., Lond.*, **75**, 295.
Henschen, S. E. (1924). *Scand. Scient. Rev.*, **3**, 10. (Quoted by Putnam.)

Kappers, C. U. A. (Quoted by Balado and Franke.)
Krause, W. (1876). "Handbuch des Menschlichen Anatomie," Bd. 1, Hahn. Hanover. (Quoted by Bruesch and Arey.)
Monakow, C. von (1905). "Gehirn Pathologie, II." Vienna.
Polyak, S. L. (1942). *J. Mt. Sinai Hosp.*, **9**, 698.
Rogalski, T. (1946). *J. Anat., Lond.*, **80**, 153.
Rönne, H. (1910). *Arch. Ophthal., Chicago*, **77**, 1.
——(1913). *Ibid.*, **85**, 489.
——(1914). *Z. ges. Neurol. Psychiat.*, **22**, 469.
——(1914). *Klin. Monatsbl. Augenheilk.*, **18**, 470.
Sántha, K. (1932). *V. Graef-Arch. Ophthal.*, **129**, 224.
Solnitzky, O., and Harman, P. J. (1946). *J. comp. Neurol.*, **85**, 313.
Thuma, B. D. (1928). *Ibid.*, **46**, 173.
Willbrand, H. (1897). *Klin. Mbl. Augenheilk.*, (Quoted by Rönne.)
Winkler, C. (1913). *Kon. Akad. U. Wetensch te Amsterdam.* Prol. Sect. Sc., **15**, Pt. 2, 840.
——(1918–1921). "Anatomie dens systeme nerveux." E. F. Bohn. Haarlem.
Woollard, H. H., and Beattie, J. (1927). *J. Anat., Lond.*, **61**, 414.
Zwanenburg, S. (1915). Inaug. Diss. Amsterdam. Quoted by Bruesch and Arey.)

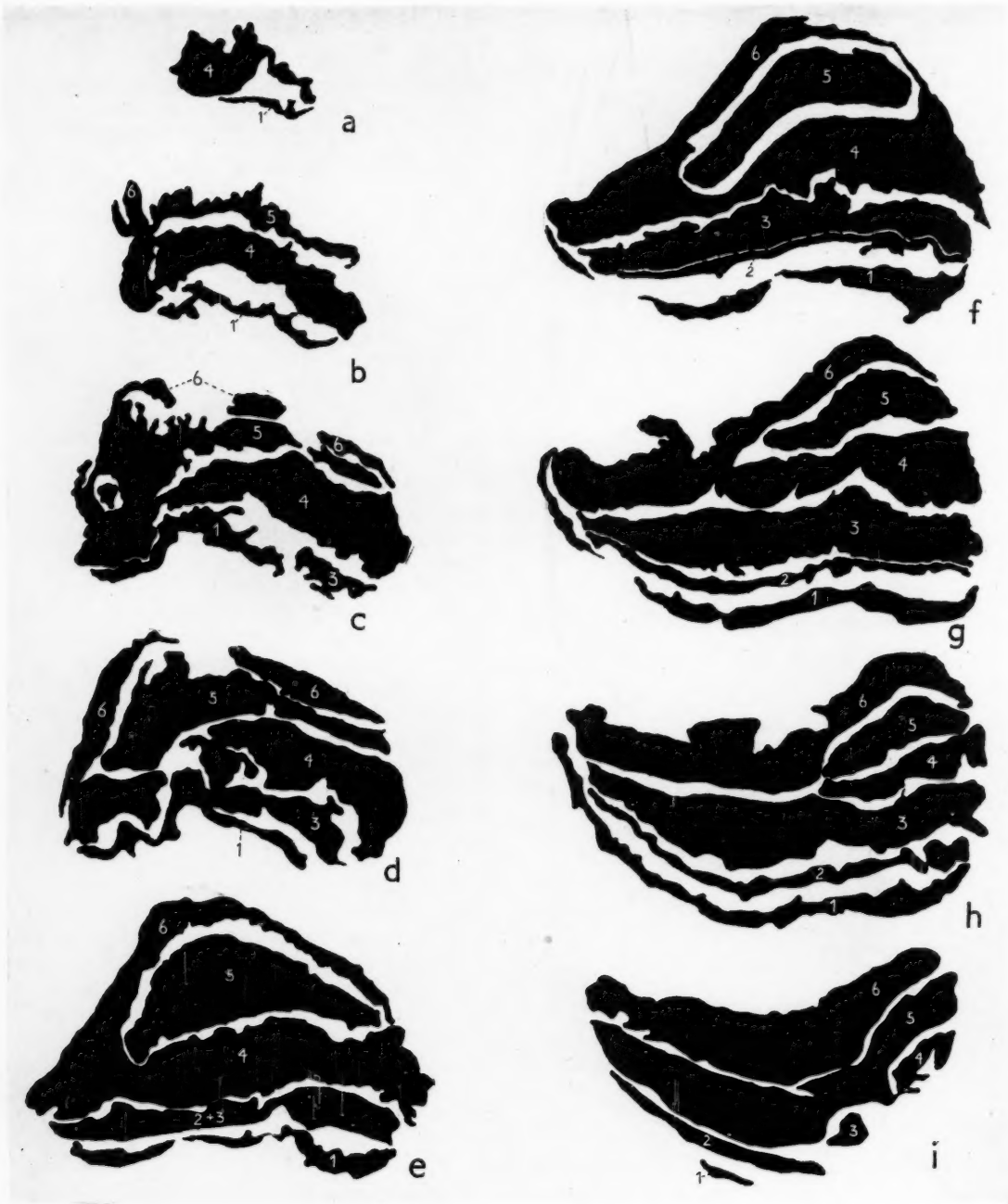

FIG. 1.—Tracings of the cell laminæ of the human lateral geniculate body made at intervals from serial transverse sections in a cranio-caudal direction. The lateral margin of the nucleus is to the left. The distances in millimetres of each section from the oral pole of the nucleus are as follows : (*a*) 0·5 ; (*b*) 1·25 ; (*c*) 1·85 ; (*d*) 2·15 ; (*e*) 2·85 ; (*f*) 3·65 ; (*g*) 4·35 ; (*h*) 5·00 ; (*i*) 6·4. Magnification +10.

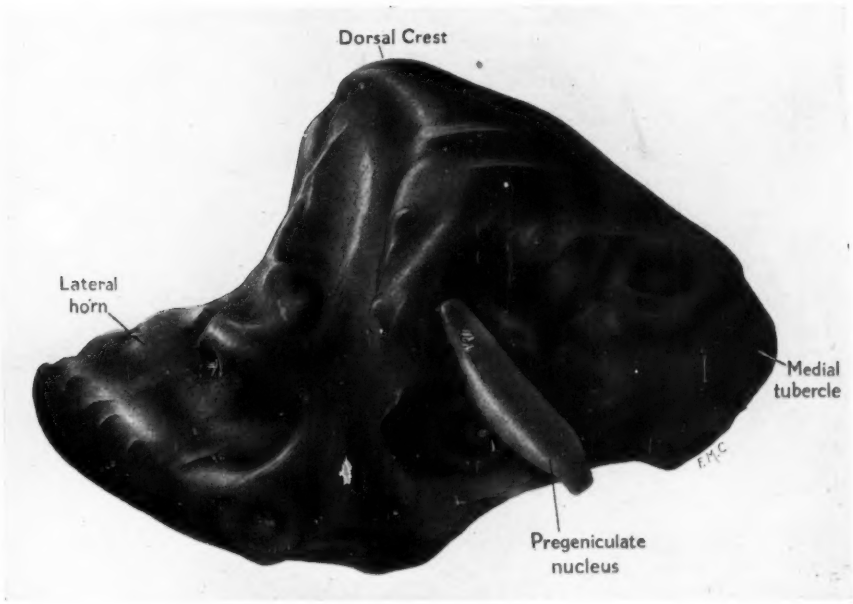

FIG. 2.—Reconstruction model of the right lateral geniculate body of a human brain, viewed from its anterior aspect. In this and other illustrations of reconstruction models, the position of the large-celled laminæ is marked with stippling.

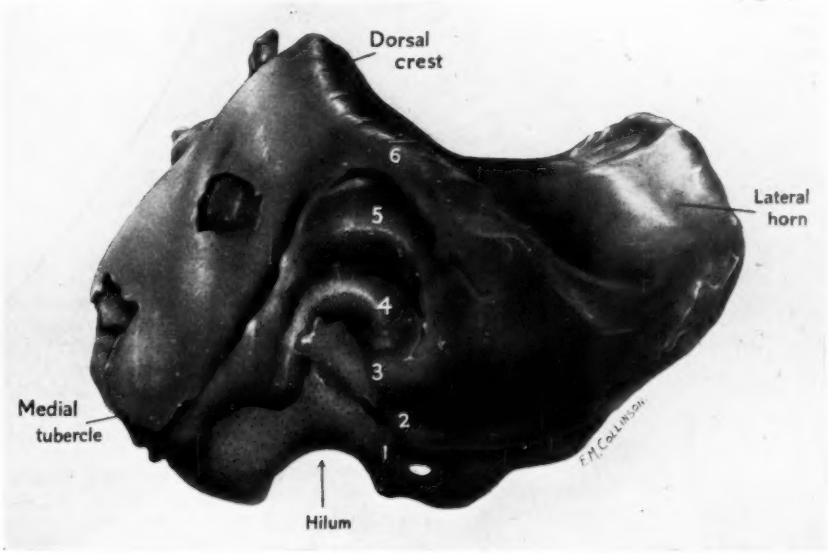

FIG. 3.—Reconstruction model of the right lateral geniculate body of a human brain, viewed from its posterior aspect. The arching of the cell laminæ to form an eversion-pattern in the main part of the nucleus is very evident. It is this arching which leads to the formation of a ventral hilum. The six cell laminæ are numbered in a ventro-dorsal direction.

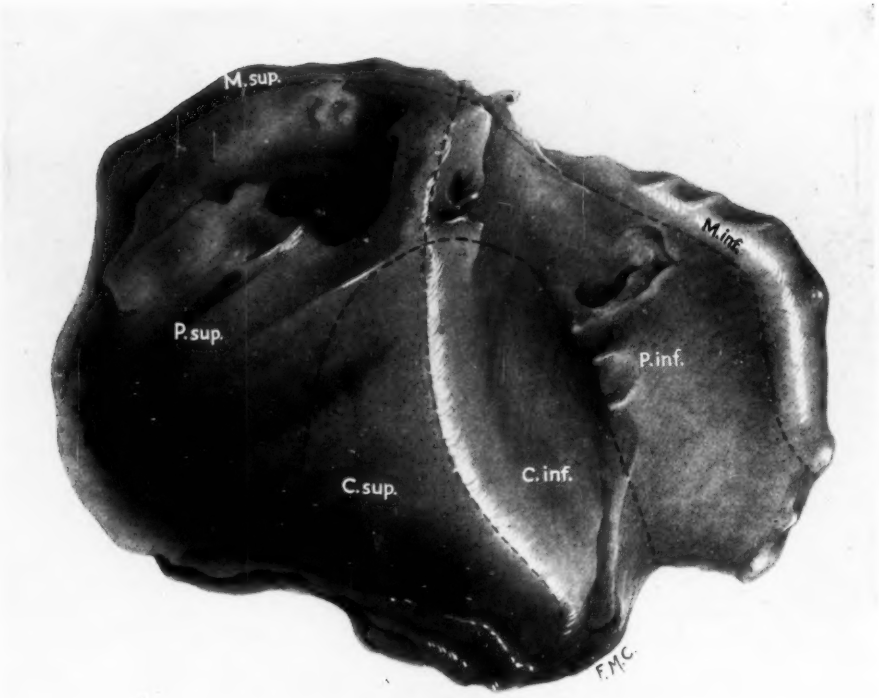

FIG. 4.—Reconstruction model of the right lateral geniculate body of a human brain, viewed from its dorsal aspect. The projection areas of the different fields of the *retina* are indicated as follows: *M. sup.* Upper monocular field; *M. inf.* Lower monocular field; *P. sup.* Upper peripheral field; *P. inf.* Lower peripheral field; *C. sup.* Upper central field; *C. inf.* Lower central field. The projection of the fixation point is at the caudal end of the central areas.

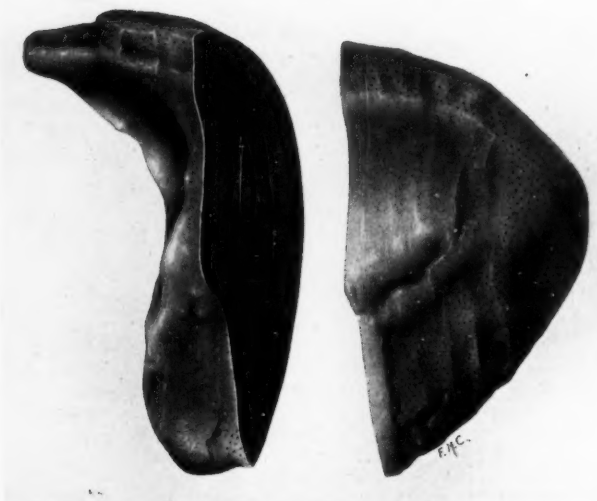

FIG. 5.—Reconstruction model of the right lateral geniculate body of *Microcebus murinus*, viewed from its medial aspect. The model has been sectioned coronally at its middle. The six cell laminæ are shown in the cut surface. Note the inversion pattern, the four small-celled laminæ being contained within the concavity of the superficially placed large cell laminæ.

FIG. 6.—Reconstruction model of the right lateral geniculate body of *Lemur fulvus*, viewed from its postero-medial aspect. Four cell laminæ are seen, disposed laterally in an inversion pattern and medio-ventrally in an eversion pattern. The latter leads to the formation ventrally of a shallow hilum.

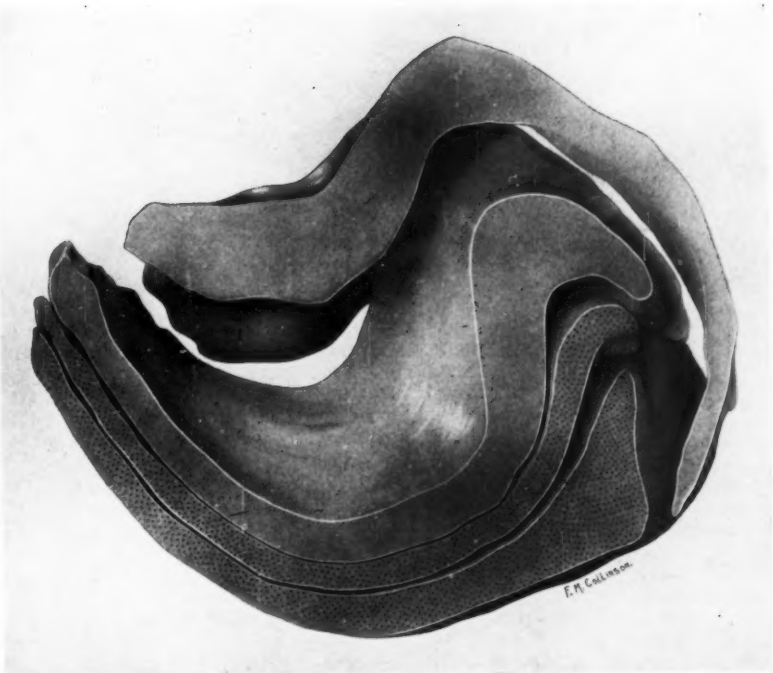

FIG. 7.—The caudal half of the reconstruction model of *Lemur fulvus* seen from in front. At this transverse level the laminæ are predominantly inverted, the two large-celled laminæ being superficial. The ventral extremities of the small-celled laminæ are everted.

FIG. 8.—Reconstruction model of the left lateral geniculate body of *Macaca mulatta*, viewed from the posterior aspect. The model has been sectioned transversely at its middle. In the plane of section, the six-laminæ pattern is found in the caudal half of the nucleus, the rostral half being composed of four laminæ only. Note that the laminæ are completely everted, the superficial large-celled layers being contained within the concavity of the deeper small-celled layers.

BOOK REVIEWS

PARAVERTEBRAL BLOCK : MINOR SYMPATHETIC SURGERY

Felix Mandl

(translated by Gertrude Kallner)

(London. William Heinemann. 1948. Pp. 330. Illustrated. Price 32*s*.)

Though the cause and cure of pain is always a central theme in medicine, the amount of active interest in it fluctuates. Before the recent war there were signs that a period of increased activity, both clinical and experimental, in this subject was beginning. The tendency was given a fillip by the material unhappily produced by the war ; particularly perhaps, by the occurrence of that most fascinating of painful states, causalgia. Dr. Mandl's book on paravertebral block, essentially a contribution to the study of pain, as he makes clear in his introduction, is therefore especially topical.

The technique and complications of the injection are adequately treated in the first part of the book. The author maintains that the unpleasant sequel of an intercostal neuritis which may follow alcohol block can be largely avoided by thorough novocaine injection before and after the alcohol. This is a point of considerable importance which requires general confirmation. The discussion of slightly differing methods is perhaps unnecessarily full and might profitably have given place to fuller descriptions of the author's own wide experience of the procedure. A useful table is included of the probable area of visceral and skeletal supply of various segments of the sympathetic chain ; though the author admits that some of this is still in dispute.

The second part of the book contains a detailed description of the diagnostic and therapeutic uses of the method. One gains the impression at times that there is scarcely a pain, be it visceral or skeletal, that does not respond to this treatment, and it is therefore a little disconcerting to find that the author does not apparently insist on control of the accuracy of injection by skin temperature measurements or sweat reactions, such as are commonly used in clinics in this country. However, in certain cases other objective changes such as rise in gastric acidity, increase in urinary output, or improvement in electrocardiogram, add confirmation to the patient's subjective report of reduction of pain. Such a report alone is an unsatisfactory criterion of physiological change, though it must often remain the chief yardstick of clinical cure when the disease itself is a complaint of pain from the patient.

The use of paravertebral block in angina pectoris is very fully discussed and the author certainly makes a case for its wide use. Successful abolition of paroxysmal tachycardia following stellate ganglion injection is also claimed. Cases of bronchial asthma which improve following sympathetic block are quoted. If such cases are confirmed after adequate control of a purely psychogenic effect, they may throw interesting light on possible cholinergic fibres in the thoracic sympathetic outflow.

The value of paravertebral block in conditions of vascular spasm of the extremities, both of veins and arteries, is stressed. But the author, in agreement with most other workers in this field, considers that the method is valueless in the treatment of hypertension or as a preliminary test for the effectiveness of later sympathetic surgery in that condition.

It will be of special interest to neurologists and neurosurgeons to read of this author's successful treatment by paravertebral block of the very troublesome condition of post-herpetic neuralgia.

The treatment of painful disorders of the extremities is dealt with at some length. Under this heading are included painful phantom limbs, causalgia, and " reflex dystrophy of the extremities," or what Livingston has termed " the post-traumatic pain syndrome." In these cases, psychogenesis and physiogenesis are closely interwoven, and it behoves us to accept with caution the claims of physical therapy. Nevertheless, the author brings forward evidence that seems to substantiate his conclusion that paravertebral block may improve or even cure the condition.

In general, the book is a useful addition to the subject. The references are full and are brought up to date in an appendix. It should be of interest to neurologists and general physicians, who, as the author points out, are quite as capable of using this technique as their surgical colleagues. But it is written by an enthusiast, and should be read in a spirit of constructive criticism.

THE PHILOSOPHY OF A SCIENTIST

R. G. Gordon

(London. Hutchinson's Scientific and Technical Publications. 1948. Pp. 206. Price 16*s*.)

This book is a sequel to one on " Personality " which the author wrote nearly twenty years ago, being an expansion of an earlier attempt to " attach some sort of meaning to the spiritual side of personality." It is a discussion of the nature of the human soul in terms of " idea " rather than of " thing," of value rather than of use. Dr. Gordon accepts the philosophy of emergence which sees mind and soul as higher qualities derived from and still dependent upon their material basis in the brain, and he believes with Alexander that Deity is also emerging as a " quality " which characterizes all that is best in man but which is only to be realized in the future through the progressive evolution of mankind.

Dr. Gordon's book is thus agnostic, rationalist, and humanist in the not ignoble tradition that leads from the Stoics through Comte to Thomas Henry Huxley, Julian Huxley, and Bertrand Russell. But its humanity and culture and gentle idealism will leave many with

some insistent questions still unanswered. Is this middle way between theism and atheism really the path of safety, or is it not rather a tightrope stretched across an abyss? Is there any logical alternative to design and chance as the causes of evolution? Does the present state of the world justify a belief in evolutionary progress, and, if there is no transcendent basis for ethics, by what standard is the humanist better than the gangster? Such questions are as old as mankind, and in these dark days we may be thankful for the light offered by humanism, even if it is unconscious of the source of the illumination which it reflects.

MODERN PSYCHIATRY IN PRACTICE

W. Lindsay Neustatter

(London. J. and A. Churchill. 1948. Second edition. Pp. vi+272. Price 12*s.* 6*d.*)

The first edition of this individual and somewhat naïve book appeared eleven years ago. The author has changed the title from "Psychology" to "Psychiatry," since in 1937 he believed the latter term insufficiently known. Some additions and alterations have been made: thus there are new chapters on post-concussional states, physical methods in psychiatric treatment, and psychopathy (the last is dealt with in four pages). His classification of psychopathies is insufficient and his discussion of the problems superficial. The chapter on hysteria has been enlarged. The author believes dissociation to be the fundamental and essential disturbance in hysteria, but in view of its frequency in other conditions this view cannot be sustained. In his attitude to hysterical amnesia, Dr. Neustatter shows himself as sceptical as most psychiatrists with service experience. The chapter on affective disorders has also been amplified; the artificial and dangerous distinction between "psychotic" and "non-psychotic" depression has been dropped. The chapter on law has also been enlarged, and there is a note on the Bourne case. There is, as before, a chapter by Mr. Jack Jennings on vocational guidance.

Although it is easy to pick holes in this book, it has the merit of freshness and vigour, and the general practitioner—for whom it is largely intended—will derive a good deal of help from its pages, particularly those dealing with child psychiatry.

THE 1947 YEAR BOOK OF NEUROLOGY, PSYCHIATRY, AND NEUROSURGERY

(Chicago. Year Book Publishers Inc. 1948. Pp. 702. Price $3.75.)

This well-known publication is useful for the busy specialist, for it reminds him of many papers he has read and draws attention to others he has "missed." In this, the 1947 volume, there are nearly seven hundred pages of clearly written abstracts, while a full index of both subjects and authors makes for convenient reference.

PSYCHOTHERAPY: ITS USES AND LIMITATIONS

D. R. Allison and R. G. Gordon

(London. Geoffrey Cumberlege; and Oxford University Press. 1947. Pp. 160+viii. Price 8*s.* 6*d.*)

It is not usual in any treatise on psychotherapy to read of contraindications to this method of treatment or any appreciation of the significance of physical factors in the production of mental symptoms. This introduction to psychotherapeutic practice is to be commended for having achieved a sensible and balanced presentation of the use of psychotherapy both in the purely neurotic patient and in those cases of psychosomatic disorder where bodily symptoms may be the sign of psychological disturbances. It will be appreciated by the general medical practitioner who is at present bewildered by the rival claims of different schools.

INTRAVENOUS METHYLENE BLUE FOR EXPERIMENTAL STUDIES ON THE CENTRAL NERVOUS SYSTEM*

BY

W. H. FEINDEL, A. C. ALLISON, and G. WEDDELL

From the Department of Anatomy, University of Oxford

(RECEIVED AUGUST 9, 1948)

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Introduction

The anatomical connexions of many of the complex fibre pathways in the brain and spinal cord still remain to be determined. Perhaps the most effective means of precisely defining these connexions is to map out, in histological sections, the degeneration of nerve cells and nerve fibres resulting from experimental or selective clinical lesions. Investigations of this nature have been dependent upon a surprisingly small range of neuro-histological techniques capable of demonstrating such degenerative changes. It is well recognized, moreover, that even these few methods, valuable as they are, suffer from certain inadequacies and involve technical difficulties which limit their usefulness to the experimental neurologist. Any new technique, therefore, which shows promise of being adaptable for this purpose is worthy of consideration.

In previous reports (Feindel, Sinclair, and Weddell, 1947, 1948) attention was drawn to the advantages for investigating the nervous system of a staining technique which is based upon the intravenous perfusion of methylene blue into an

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anæsthetized animal, and which permits a wide application of this dye as an intravital stain selective for nervous tissue. This technique has now proved of value in a number of studies on the peripheral and autonomic nervous systems, including the neural patterns in skeletal muscle, cornea, skin, and epiglottis (Feindel, 1948); the neural basis of pain sensibility in deep somatic tissues (Feindel, Weddell, and Sinclair, 1948); the innervation of the iris (Hinshaw, Feindel, and Weddell, 1948), and the nerve supply of blood vessels (Millen, 1948).

In regard particularly to the central nervous system, the intravenous method makes possible the perfusion and uniform staining *in vivo* of the entire brain, which may then be removed and prepared for microscopic examination as frozen or paraffin sections. With this method it has already been possible to demonstrate in the normal brain cytological details such as *boutons terminaux* on cortical ganglion cells and on mitral cells in the olfactory bulb, which can be impregnated only with difficulty (Meyer and Meyer, 1945; Gibson, 1937) by specialized silver techniques.

More recently (Feindel and Allison, 1948), it was found that the intravenous methylene blue method is capable of giving a striking picture of nerve fibre degeneration following experimental lesions of the brain. In rabbits perfused with a relatively small quantity of concentrated solution of the dye five days after enucleation of one eye, degenerating fibres in the optic nerve and contralateral optic tract are easily recognized macroscopically by their intense and metachromatic staining, which is conspicuously different from that of normal fibres. On microscopic examination the degenerating axis cylinders show, in addition, morphological changes such as blistering and fragmentation which render them clearly distinguishable from the normal.

These two main features of intravital methylene blue, the selective staining of normal nerve tissue and the differential staining of degenerating neuronal elements, endow the intravenous technique with considerable potentialities as an experimental method for anatomical research on the central nervous system. The purpose of this report is to discuss these potentialities on the basis of results obtained so far from studies of experimental degeneration in the optic system of the rabbit. It should be emphasized that the actual method used at the present stage of our investigations, although satisfactory for some purposes, is not yet sufficiently critical for all types of experimental material from the central nervous system, and, indeed, it is still in the process of modification and improvement.

Review of Other Methods

In order to evaluate the possible advantages of the intravenous method, it will be compared at many points throughout this paper with experimental methods previously developed for investigating the anatomy of central fibre pathways. Some aspects of these techniques have been discussed at length (Walker, 1938; Fulton, 1943; Clark, 1945) but no review which considers, for example, the recently developed silver technique for demonstrating terminal degeneration (Glees, 1946), has yet been made. It therefore seems desirable to outline here the main features of these other techniques.

Marchi Method.—A great part of our basic anatomical knowledge of the pathways in the central nervous system has been provided by the use of the technique introduced by Marchi and Algeri (1885), which depends upon the observation that the products of degeneration of myelin sheaths can be stained black by osmic acid, while staining of the normal myelin can be prevented by preliminary treatment with a chromic salt. The distribution of the degenerating tracts, if their fibres are closely packed, can be readily outlined macroscopically, and can be traced in considerable detail by microscopic examination of serial sections. A serious limitation of the method is its deficiency in demonstrating degeneration in non-myelinated or finely myelinated fibres, for fibres of this size may constitute a large proportion of such important pathways as the spinothalamic tract (Håggqvist, 1936), the medullary pyramidal tract (Lassek and Rasmussen, 1939), many of the pathways projecting to and from the hypothalamus (Fulton, 1943), and the projections from the cortical suppressor areas to the basal ganglia (Glees, 1944). Indeed, by the widespread use of the Marchi technique, neurologists have perhaps tended to overlook the significance of small myelinated and non-myelinated fibres in many tracts of the central nervous system.

In addition, since even myelinated fibres may become divested of their myelin sheaths some distance before they end, as, for example, in the case of the collicular fibres of the optic system, their terminations cannot be conclusively determined by this method. Neither can terminal fibres be distinguished with assurance from fibres of passage. Moreover, myelinated fibres may frequently give off small myelinated or non-myelinated collaterals (Ramón y Cajal, 1928) which may not be rendered visible by the Marchi stain.

A further inherent disadvantage of the Marchi reaction is that the course of the degenerating fibres is indicated mainly by granular tracks of myelin débris and not by actual staining of the intact axis cylinder. Thus it is almost impossible to observe the site and extent of axone branching or to estimate the size of degenerating fibres.

Finally, despite numerous improvements and modifications (Mettler, 1932; Swank and Davenport, 1934, 1935; Glees, 1943) the method still remains, from a technical standpoint, a highly variable and capricious one. It requires great care in order to obtain specific staining of degenerating fibres and to avoid pseudo-Marchi

precipitation, which is capable of simulating degeneration in apparently normal fibre tracts.

Nissl Methods

RETROGRADE CELL DEGENERATION.—It was first noted by Nissl (1892) that when an axone is cut its nerve cell undergoes characteristic changes, including at first chromatolysis, followed by atrophy and glial replacement. This process of retrograde cell degeneration provides, in certain situations, an accurate means of tracing the origin of fibre tracts, but the method has several important limitations.

The cells from which a tract is derived must be compactly grouped so that the zone of atrophy can be recognized in histological sections. This arrangement seems to hold particularly for the thalamic nuclei which send projections to the cerebral cortex, and the method has proved of great value in experienced hands for the study of thalamo-cortical connexions, both in experimental (Clark, 1932; Walker, 1938) and in clinical material (Meyer, Beck, and McLardy, 1947). The method is not a particularly sensitive one and is of little use for studying fibre tracts, such as the cortico-cortical association pathways, whose cells of origin are more diffusely arranged. Furthermore, retrograde cell changes may not necessarily occur at the same time interval in neurones in various parts of the central nervous system, and the optimum period must be determined for each fibre system studied. In addition, some nerve cells show little demonstrable alteration after a lesion (Walker, 1938), and the cell bodies of certain neurones, for example in the supraoptic nucleus, normally have an appearance which simulates chromatolysis. The occurrence of axone bifurcation in central fibre tracts may also complicate the situation, since section of a collateral branch may cause little or no change in the parent cell (Ramón y Cajal, 1928).

TRANSNEURONAL CELL DEGENERATION.—The process of transneuronal, or better, trans-synaptic degeneration can also be studied by Nissl stain. Since this phenomenon depends upon the fact that a nerve cell becomes atrophied when the fibre ending on it has degenerated, it provides a basis for defining the site of termination of nerve fibres. Unfortunately, trans-synaptic changes are known to occur in relation to only a few neuronal systems, and seems to be related to the rather special circumstance that each nerve cell concerned is entirely dependent for its afferent influence upon its contiguity with a single terminal fibre.

The method has been applied successfully to studies on fibre termination in the lateral geniculate body of monkey (Minkowski, 1920; Clark and Penman, 1934), and man (Clark, 1942).

STAINING OF FIBRE TRACTS.—The basic dyes used in the various modifications of the Nissl technique are taken up only by the cell bodies and the immediate processes of neurones. Since neither the myelin sheaths nor the axis cylinders of normal or degenerating fibres are stained, the method is not primarily applicable for studying the course of fibre paths. Some compact fibre tracts such as the prefronto-pontile (Arnold's) bundle may, however, often be traced in thickly cut celloidin sections stained with the Nissl technique, by following the track of dense gliosis and increased vascularity resulting from degeneration (Meyer and others, 1947).

MODIFIED GUDDEN METHOD.—If experimental lesions are made in the brains of young or newborn animals, the retrograde atrophy and cell loss takes place more rapidly than in older animals, and eventually leads to the formation of a glial scar which grossly indicates the localization of the lesion. This method, originally introduced by Gudden in 1870 (see Fulton, 1943), has had only moderately successful use. Recently, however, Brodal (1940) has made an intensive study of the method, and by adopting a shorter post-operative survival time has found it possible to utilize the marked early cell changes while eliminating the undesirable distortion of the later gliosis. This modification appears to make the method more sensitive, and in spite of its disadvantages, such as the difficulties of producing accurately placed lesions in the brains of young animals, it has proved of value in studies of the olivocerebellar connexions and the anterior commisure (Brodal, 1940, 1948).

Silver Methods.—Silver impregnation techniques have been used for many years by the Spanish school of histologists for demonstrating degenerative changes in nerve fibres. The enlargement and deeper degree of staining which terminal *boutons* show during degeneration have been utilized by Hoff (1935), Gibson (1937), and others for the purpose of anatomical localization of fibre termination. However, the successful impregnation of *boutons*, particularly in nervous tissue from supra-spinal levels, is a difficult technical feat and for a number of reasons the results based upon the interpretation of degenerative changes in *boutons terminaux* have not been accepted as entirely conclusive by all workers. Fulton (1943) has given an excellent review of this somewhat controversial question. More recently, a silver method developed by Glees (1946), which demonstrates not only boutonal endings but also the more conspicuous preterminal and terminal parts of degenerating nerve fibres, has proved invaluable as a means of studying the ultimate distribution of central fibre tracts. Although this method overcomes many deficiencies of the Marchi technique, in that it gives evidence of the precise terminal distribution of non-myelinated as well as myelinated degenerating fibres, its application also presents a number of difficulties. Terminals in normal tissues are notoriously subject to variation (Phalen and Davenport, 1937; Minckler, 1942). For this reason, areas in which it is expected that degeneration will be found must be carefully compared with corresponding normal control areas. Furthermore, slight alterations in the picture of terminals must be disregarded as being possibly within the range of normal variation. Only well-marked changes can be accepted as conclusive evidence of experimental degeneration. The time limits during which such changes are optimally

demonstrated by silver impregnation are quite narrow, usually from 4 to 7 days postoperatively, and this factor restricts the range of clinical autopsy material which can be studied.

These features, together with the fact that the technique itself, like most metallic methods, is painstaking and time-consuming, tends to limit its scope to tracts which terminate in relatively small topographical areas. The application of such a method also requires both a high degree of technical skill for the preparation of reliably impregnated sections, and an intimate experience of the experimental material in order to interpret the histological findings. It has been applied with valuable results to studies in experimental animals on the termination of the optic tract (Glees and Clark, 1941), the cortico-striate connexions (Glees, 1944), and the olfactory tract (Clark and Meyer, 1948). In human material after leucotomy, it has been used to define the corticofugal connexions of the frontal lobe (Meyer and Crawford, 1948).

Comment

LIMITATION OF PRESENT METHODS.—In summary, it may be stated that each of the above-mentioned techniques has its own particular advantages. All except the silver technique have been exploited for many years. The fact that so little (and often conflicting) information is available about the detailed neuro-anatomy of many important pathways in the central nervous system is in itself evidence of their limitations. It is surprising, for example, that the anatomical connexions of the temporal lobes are largely unknown (Walker, 1938; Fulton, 1943) although, on physiological and psychological grounds, their role in the higher mental organization of the individual is undoubtedly of the utmost importance (Penfield, 1946; Clark, 1948).

PHYSIOLOGICAL NEURONOGRAPHY.—Although not a histological technique, the method of physiological neuronography should be briefly mentioned. This technique (see McCulloch, 1944) depends upon the mapping out of large electrical potentials propagated as a result of the excitation of a local area of the brain by application of strychnine and has recently brought about advances in experimental neurology so remarkable that they have opened up a completely new approach to this field of study. However, in most cases, the anatomical basis for the nervous pathways along which these potentials travel still remains to be defined.

The results which have been obtained so far by the use of intravenous methylene blue on the central nervous system suggest that this method, if it is found to give consistently satisfactory results, may be a useful supplement to the experimental anatomical methods now available.

Material and Methods

Operation.—Young male and female rabbits weighing 1 to 1·5 kilogrammes were used in the present study. Enucleation of one eye was previously selected (Feindel and Allison, 1948) as a convenient control lesion for evaluating the staining method because the operative trauma is entirely extracranial and the anatomical features of the primary optic pathways are fairly well established (Clark, 1942; Fulton, 1943).

In each of eight animals one eye was removed under ether anæsthesia, with care to prevent traction on the optic nerve. Hæmostasis was secured by warm saline packs. Penicillin-sulphamezathine powder was then insufflated into the orbit and the lids closed by several interrupted silk sutures. The wounds were examined at autopsy and without exception were found to be free from infection and post-operative hæmorrhage. In two more animals, in addition to the removal of the eye, a unilateral olfactory tract section was made through an orbital approach. Normal brains from ten animals which were injected for the study of tissues other than the central nervous system were also available for comparative studies.

Injection of Dye.—At intervals varying from twenty-four hours to twenty days after operation the animals were lightly anæsthetized with intravenous nembutal (35 mg. per kg. of body weight) and given methylene blue (supplied by British Drug Houses Ltd.), in 0·9 per cent. physiological saline, by the intravenous drip technique previously described (Feindel, Sinclair, and Weddell, 1947).

However, in the present investigation, a more concentrated solution of the dye, up to 2·5 per cent., was used in order to decrease the volume of fluid injected and to obviate the risk of cerebral œdema. A large dose of the dye (300 to 500 mg. per kg. of body weight) was deliberately administered during the early experiments, but it is now clear that much smaller dosages may be adequate. The injection was regulated at 2 to 6 drops per minute, depending upon the concentration of the dye solution, and was usually prolonged for one to three hours. At the end of this time the animals were killed by a rapid overdose of a few c.cm. of the dye, or by an overdose of nembutal, or, in a few cases, by section of the medulla.

Histological Preparation.—The brain was then removed and immersed in a chilled solution of 6 per cent. ammonium molybdate, made up in 0·9 per cent. saline as suggested by the work of Cole (1946). Penetration of the molybdate into the brain tissue, which ensures uniform fixation of the dye, will occur to a depth of not much more than one centimetre. Sections of the brain were therefore cut at rather less than that thickness with a sharp razor blade, taking great care to

avoid distorting the tissue. Adequate fixation of the dye can be assured by keeping the tissue slices in the refrigerator at 0° to 2° C. for a period from two to sixteen hours, varying with the size of the specimen. After thorough washing in several changes of chilled saline (0·9 per cent.) for a period of fifteen to twenty minutes, the brain sections were kept in 10 per cent. neutral formol-saline for a period which, it was found, should not exceed three days. Frozen sections could then be cut and, after dehydration and clearing in xylol, mounted in neutral balsam.

Most of the tissue studied, however, was washed after formalin fixation and dehydrated in alcohol, using generous quantities and rapid changes to eliminate loss of dye. Some blocks were then cleared in xylol and embedded in paraffin, but it was later found that embedding by the double celloidin-paraffin method of Peterfi (see Romeis, 1924) gave superior preparations. The tissue blocks, when embedded, are a deep blue colour. They may then be sectioned and, without further staining, taken directly through xylol, alcohol and xylol, and mounted in neutral balsam.

The reagents most likely to dissolve out the stain are the ethyl alcohol and the solution of celloidin in methyl benzoate. The tissue blocks should be taken through these stages as rapidly as possible. Mounted sections, in spite of exposure to intense light for photographic purposes, are resistant to fading for many months.

Observations

Macroscopic Features

STAINING OF NORMAL BRAIN.—On removal of the calvarium the surface of the brain is usually pale blue but gradually darkens on exposure to air, until the entire brain appears deep blue in colour (Fig. 1). Some areas darken more rapidly than others, and in the early stages this gives a blotchy appearance to the cortex, with pale areas standing out, as for example, in the temporal poles of the brain illustrated in Fig. 2.

When the fresh brain is sliced, the "blueing" is seen to be confined to the external surface, although the cut surface soon becomes blue in turn. Adequate immersion in molybdate solution brings about a more even blueing of the dye throughout the entire block of tissue.

Grey matter is stained more deeply than white matter, so that normal fibre tracts, such as the corpus callosum and the internal capsule, remain pale (Fig. 3).

STAINING OF DEGENERATING FIBRE TRACTS.—Degenerating fibres take up the stain as intensely as grey matter and exhibit, in addition, a distinct purplish tinge. This deeper and metachromatic staining permits the ready identification of the degenerating optic nerve and outlines the bundle of crossed degenerating fibres in the optic tract (Figs. 1, 2, and 3). In the two instances in which an additional lesion in the olfactory tract was made, the definite purplish colour of the degenerating fibres provided sufficient contrast with the deep blue of the surrounding normal cortex to mark out by naked eye examination the distribution of olfactory fibres in the piriform area.

A further observation is that the differential staining of the degenerating fibres loses none of its distinctness as late as twenty days after removal of the eye (Figs. 2 and 3). Weddell and Glees (1941), injecting methylene blue locally, showed that degenerating fibres in cutaneous nerves are not stained by the dye later than fourteen days after experimental section. This difference may be due in part to the more rapid removal of degenerating neuronal products in the periphery, as compared to the central nervous system.

Microscopic Features.—The prepared sections of the brain have much the same appearance to the naked eye as sections stained by the ordinary Nissl technique. On microscopic examination the most outstanding features are the staining of the cell bodies and immediate processes of the neurons, the slight degree or absence of staining of normal fibre tracts in most regions, and the conspicuous differential staining of degenerating nerve fibres.

NERVE CELLS AND INCLUSIONS.—Cytoarchitectonic differences in basal ganglia and cortical areas are sufficiently clear to allow their satisfactory identification, as, for example, the retrosplenial cortex shown in Fig. 9. Indeed, because there is some staining of matrix as well as cell bodies, differences between adjacent cell masses and layers are often more marked than in sections stained by the standard Nissl techniques (Fig. 29). Moreover, in many cases, satisfactory analytic staining of normal neurones clearly showing the finest ramifications of their axons and dendrites, as well as their nuclei, are obtained.

Usually the cytoplasm of neurones appears a homogeneous, clear, light pastel blue colour. In certain situations, however, a large number of fine blue granules are scattered throughout the perikaryon and along the axone, as shown in Figs. 27 and 28. In some cells there is superimposed upon this fine granulation a mass of coarse, dark-blue spherules, often inter-connected and closely packed about the nuclear region of the cell (Fig. 27).

The possible significance of these structures will be discussed below.

NORMAL NERVE FIBRES.—Normal nerve fibres are usually unstained but may occasionally be stained a green-blue colour. In some regions, for example the pons, the fibres show a smooth, evenly stained, wire-like appearance (Fig. 15), while in other areas, such as the internal capsule, they may sometimes present smooth ovoid varicosities (Fig. 16).

DEGENERATING FIBRES.—Degenerating fibres, on the other hand, are distinguished readily from normal fibres by their intense purplish shade of staining and by the morphological changes described below. These features render them conspicuous even under low-power magnification so that their main course and distribution may be rapidly traced in serial sections (Figs. 4, 5, and 10).

Under high magnifications, the degenerating fibres, with their purple staining (Figs. 7 and 8) and distorted outline (Figs. 11, 12, 13), are strikingly different from normal fibres (Fig. 15).

Characteristic Changes.—Many stages of fibre degeneration are present five days after the experimental lesion. The change in staining reaction probably takes place early, since many fibres with minimal distortion in outline have a distinct purple colour. This was suggested by studies in the peripheral nervous system where metachromasia occurs very soon after section of a cutaneous nerve (Weddell and Glees, 1941). Prominent varicosities appear at intervals along the swollen axis cylinders, and at a later stage these varicosities enlarge into round vesicular masses strung along the irregular swollen axones (Figs. 21, 22). The ballooned vesicles may reach an astonishing size and often appear hollow or reticulated (Figs. 12, 13). A characteristically blistered and purple axone is shown in Fig. 7. Finally, axones and vesicles lose their solid, densely stained appearance, become more lightly stained and mesh-like, and eventually disintegrate into coarse, irregular fragments. The vesicles often persist as isolated spherules with no apparent axonic thread connecting them (Fig. 13). Throughout all stages of degeneration the metachromatic staining is maintained, even for the fragments and granules of axones. It is of interest that these morphological changes in degenerating fibres as demonstrated by intravital methylene blue are almost identical with those described by Cajal (1928), who used the reduced silver nitrate technique, for many parts of the central nervous system including the primary optic pathway.

Site of Degeneration.—Five days after the lesion degenerative changes appear, in general, to be most advanced toward the termination of the optic tract, that is, in areas most remote from the lesion. This observation conforms with those obtained by Meader (1939), using the Marchi technique.

Fibre Sizes Affected.—Even making allowance for the degenerative changes, considerable variation of axone size is demonstrated in the optic tract. The degeneration at five days appears to affect the entire spectrum of fibre sizes, although it is more pronounced in the larger fibres. Some medium and small fibres may show granular fibrillated axones, sometimes without the formation of vesicles. But a number of individual fibres of the very finest diameter show ovoid swellings strung along an axone undergoing early fragmentation (See Figs. 6, 8, 11, 12, 13).

Again, in a general way, no sorting out of fibre sizes seems to occur at the level of the lateral geniculate body, and the fibres coursing on to the mid-brain are not necessarily those of the smallest diameter (Fig. 14). It is obviously necessary, however, for this observation to be substantiated by further study, particularly of material at shorter postoperative intervals and after minimal retinal lesions. The wide range of fibre size which is apparent in the material is illustrated in Figs. 6, 11, and 14 and no doubt provides a morphological basis for the differences of conduction velocity in the optic fibres which have recently been summarized by O'Leary (1944).

Fibre Bifurcation.—As in the peripheral nervous system, the intravenous methylene blue stains the individual degenerating axis cylinders. For this reason degenerating fibres may be traced for considerable distances. The precise course and direction of the axones are therefore readily determined (Figs. 6, 11). Collateral fibres are boldly outlined, for example, where they run towards the dorsal nucleus of the lateral geniculate body (Figs. 5, 11, 14), and the axone branching where these collaterals originate can usually be found (Figs. 10, 12, 14, 19, 20).

Node Formation.—At the site of axone branching a definite node-like formation may be seen, which often takes the form of a cuff placed just at the angle of the dividing axone (Figs. 19, 20), a picture very similar to that obtained by methylene blue and silver stains in the periphery. Constrictions may also be seen along the course of axis cylinders, and these too are suggestive of nodal structures (Fig. 17). It is of some interest, as Cajal (1928) observed with

silver stains, that swelling of the axoplasm during degeneration may first take place on either side of such a nodal constriction (Fig. 17). Further evidence for the existence of nodes in the central nervous system has been the presence at intervals along the purple degenerating axone of cuffs which are distinguished by their intense degree of staining and their green-blue coloration (Fig. 18). Although nodes on normal fibres in the central nervous system have been beautifully figured and described by Cajal (1911, 1928), for example, in the optic nerve and spinal cord, the present-day scepticism concerning their existence has prompted us to re-emphasize this finding in the light of the present observations (Allison and Feindel, 1948).

Degenerating Preterminals and Terminals.—The preterminal portions of the degenerating fibres, as well as the actual terminal *boutons*, may be stained both in the lateral geniculate body and in the midbrain. The preterminals may appear as strings of solid or vesicular beads among the ganglion cells upon which they terminate (Figs. 8 and 23). The normal terminals (Fig. 24) are small swellings which, at one level of focus under high magnification, appear as ring formations on the surface of the cells. Degenerating terminals take the form of enlarged solid plaques, which stain deeply with methylene blue (Figs. 25, 26). The appearance of the normal as well as the degenerating *boutons terminaux* corresponds closely to the picture obtained by the silver technique of Glees (Meyer and Meyer, 1945) or the double impregnation method of Hortega (Gibson, 1948). It has already been pointed out that the critical staining of such fine terminals by intravenous methylene blue may be related to the fact that the stain is applied to living nervous tissue (Feindel, Sinclair, and Weddell, 1947).

Non-nervous Structures.—Brief mention may be made of non-nervous structures stained by the same technique. Cerebral and intracerebral blood vessels are satisfactorily demonstrated. With heavy doses of dye, it is also possible to obtain staining of neuroglial elements. Thus the cell-bodies and processes of astrocytes, particularly in the region of small intracerebral blood vessels, may take up the dye. In addition, ependymal cells of the ventricular lining may stain selectively so that their unipolar processes can be seen extending into the cerebral tissue (Fig. 30).

Discussion

Previous Studies on Intravital Methylene Blue.—It should be noted that the general features of intravital methylene blue technique have by now become well established by numerous studies on the peripheral nervous system, which have been summarized by Dogiel (1926), Schabadasch (1935, 1936), and Weddell and others (1940). The fact that degenerating fibres in the periphery may be differentially stained by intravital methylene blue has been recognized for some time and utilized in a number of studies, including the innervation of the neuromuscular spindle (Hines and Tower, 1928), the origin of the fibres supplying Pacinian corpuscles in the mesentery (Sheehan, 1933), and the distribution and pattern of cutaneous nerve fibres and endings in experimental animals and man (Weddell, 1945). The early stages of degeneration in cutaneous nerve fibres have been studied in detail, using both vital methylene blue and silver methods, by Weddell and Glees (1941).

It is of historic interest that Ehrlich (1886), in his original paper on the use of methylene blue as a stain for living nerve tissue, described staining of nerve fibres in the medulla and cerebrum as well as pericellular networks of fine nerve fibrils in relation to cortical ganglion cells. Cajal (1911) placed great importance on methylene blue as an analytic stain for studies on the normal brain, and the many finely executed illustrations in his classic textbook indicate the remarkable success he achieved in applying the method. In his studies of nerve degeneration, in both the peripheral and central nervous systems, however, Cajal (1928) relied almost exclusively upon silver impregnations, dismissing the methylene blue method of Ehrlich because of his early observation (Cajal, 1896) that the results were uncertain and obtained only with difficulty. Reference to any other serious attempt to study fibre degeneration in the central nervous system by vital methylene blue has not been found (Feindel, 1948).

Advantages of the Intravenous Technique.—Many of the advantages and possible developments of the intravenous method which have been discussed with particular reference to the peripheral nervous system (Feindel, Sinclair, and Weddell, 1947) also apply to the technique as used for experimental studies on the central nervous system. Two main features are evident from the results described above. In the first place, almost the entire neurone —cell-body, cytoplasmic inclusions, axis cylinder, and terminals—may be demonstrated. Secondly, degenerating axones, preterminals, and terminals are conspicuously differentiated from normal axis cylinders.

Staining of Nerve Cells and Cellular Inclusions.—The staining of nerve cells as a

whole implies that the method may be developed as an analytic stain for normal central nervous tissue, serving to some extent as a substitute for the uncertain Golgi technique. Reference has already been made to Cajal's use of the method for this purpose, and similar brilliant results have been obtained more recently by Polyak (1941) in his well-known studies on the neuro-cytology of the retina. Many other structures of the normal neurone, such as the nodes of the axis cylinders and the peri-cellular terminals, are demonstrated.

The staining of granular inclusions within the cytoplasm of normal nerve cells, which show considerable resemblance in distribution and character to mitochondria and Golgi apparatus, is of some interest. Methylene blue has been used not only as a supravital stain for mitochondria and Golgi apparatus (Worley and Worley, 1943) but also as a stain for such intracellular substances as ribonucleoprotein (Wislocki and Dempsey, 1948). These observations suggest that the intravenous method, by virtue of being applied to living nervous tissue, may possibly be elaborated into a cytological technique for studying nerve cell inclusions. Since it is well known that cytoplasmic inclusions are intimately related to the metabolism and activity of the cell, the method may perhaps also be utilized as an indicator for the functional activity of different nerve cell groups. Indeed, Ehrlich (1885) was led at first to use methylene blue, not because of its histological value, but for indicating the level of metabolic gradients in different tissues of the living animal. Moreover, a number of most suggestive observations have been made on the pharmacological antagonism of intravital methylene blue and acetylcholine (see, for example, Cook, 1926) and it is not improbable that the vital staining of fine nervous terminals may be related to the high content of acetylcholine present in association with nerve endings (Nachmansohn, 1939). Further work along these lines is clearly indicated.

STAINING OF DEGENERATING FIBRES.—The ready identification of degenerating fibres by their metachromatic purple staining and by their characteristic vesiculation and swelling is also a feature of fundamental importance. The feasibility of identifying degenerating fibre tracts in macroscopic sections is of value in that it may provide an indication of the main areas to which a fibre system is distributed. Thus, it may serve as a useful complementary technique to silver methods, which are impractical for exploring very extensive regions of the brain. In microscopic sections, the individual degenerating axones can also be identified not only in their main course but even towards their terminations.

SIGNIFICANCE OF AXONE BRANCHING.—The method provides a means for noting axone bifurcation and for tracing collateral fibres, for example, where they sweep from the optic tract into the dorsal nucleus of the lateral geniculate body. The site and mode of axone branching in the central fibre tracts is a subject which has received remarkably little direct study, although it is a neural mechanism which may provide a great degree of flexibility for fixed anatomical pathways in the central nervous system. Thereby, functional connexions may be established by a single ganglion cell with different regions of the central nervous system which are widely separated.

The occurrence in the peripheral nervous system of such axone branching, which allows one nerve cell to have endings in two widely separated areas of skin, is implied by the work of Adrian and others (1931), and the significance of this axonal arrangement in providing an anatomical explanation of the mechanism of referred pain has recently been emphasized (Sinclair, Weddell, and Feindel, 1948).

Sherrington (1892) noted the incidence of geminal or bifurcating myelinated fibres in various parts of the brain and spinal cord. Cajal (1911) confirmed Nansen's classical studies on the division of dorsal root fibres in the spinal cord, and contributed observations of his own on fibre bifurcation in many regions of the brain stem and in the subcortical white matter. O'Leary (1944), with particular reference to the optic system, has recently described the influence which such axone branching may have on the character of electrical responses from central fibre tracts. In the present material, extensive axone division appears to take place at the level of the lateral geniculate body, with some branches coursing towards the dorsal nucleus (Figs. 5, 10, 11, 14) and others running on towards midbrain nuclei. In both regions many axones, before their final termination, also frequently show branching (Figs. 19, 20). Cajal (1911) by the use of Ehrlich's methylene blue method in the rabbit, found axone bifurcation in a small number of fibres in the optic chiasm, one branch passing backwards into each optic tract.

Fibre branching of this nature is obviously of relevance in anatomical studies of the visual pathway, for example, in the determination of the ratio of retinal ganglion cells to optic fibres. Furthermore, such a mechanism may provide an actual anatomical basis for a number of phenomena related to the bilateral representation of the visual pathways, such as macular sparing, which have heretofore been unsatisfactorily explained.

COMPARISON WITH OTHER METHODS.—In a general way, then, the method gives promise of combining some of the advantages of all three main histological techniques at present in use for experimental studies on the central nervous system.

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Methylene blue has also been one of the standard basic dyes used for the ordinary Nissl method, and the staining of the cell bodies and cytoplasm of the neurones by the intravenous methylene blue is therefore not surprising. This feature is particularly useful in experimental material in that it makes it possible to ascertain, in the same preparation, the relationship of fibre tracts to groups of ganglion cells, but the potentialities which it may offer for critical demonstration of retrograde or transneuronal cell changes have yet to be determined.

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IMPROVEMENT OF TECHNIQUE.—At present the successful preparation of material depends upon three essential points: (1) the slow perfusion of sufficient dye into the animal to produce staining of the central nervous system; (2) the uniform oxidation and fixation of the dye; and (3) the histological fixation of the tissue itself. Since further investigations on these points are still in progress, only brief mention will be made of them.

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Many of the procedures recommended for intravital methylene blue staining have become overwhelmingly complex, and a careful re-evaluation of the factors which tend to give more specific staining has been made by Heller, Thomas, and Davenport (1947) in relation to the supravital immersion technique. It is of interest to note that the optimum conditions they suggest, such as oxygenation and buffering of staining solutions, the use of solutions at body temperature, and the addition of essential ions and dextrose to the staining solution, are conveniently met by introducing the dye slowly into the blood stream of the living animal.

INTRAVITAL STAINING OF EMBRYOS.—In these studies on the central nervous system, methylene blue has passed readily through the so-called blood-brain barrier, and in connexion with this a further development of the technique should be mentioned. Although earlier work (Goldmann, 1909; Wislocki, 1920, 1921) has shown that colloidal dyes, such as trypan blue, pass from the maternal blood only in sufficient quantities to stain the embryo slightly or not at all, the prolonged

demonstrated by silver impregnation are quite narrow, usually from 4 to 7 days postoperatively, and this factor restricts the range of clinical autopsy material which can be studied.

These features, together with the fact that the technique itself, like most metallic methods, is painstaking and time-consuming, tends to limit its scope to tracts which terminate in relatively small topographical areas. The application of such a method also requires both a high degree of technical skill for the preparation of reliably impregnated sections, and an intimate experience of the experimental material in order to interpret the histological findings. It has been applied with valuable results to studies in experimental animals on the termination of the optic tract (Glees and Clark, 1941), the cortico-striate connexions (Glees, 1944), and the olfactory tract (Clark and Meyer, 1948). In human material after leucotomy, it has been used to define the corticofugal connexions of the frontal lobe (Meyer and Crawford, 1948).

Comment

LIMITATION OF PRESENT METHODS.—In summary, it may be stated that each of the above-mentioned techniques has its own particular advantages. All except the silver technique have been exploited for many years. The fact that so little (and often conflicting) information is available about the detailed neuro-anatomy of many important pathways in the central nervous system is in itself evidence of their limitations. It is surprising, for example, that the anatomical connexions of the temporal lobes are largely unknown (Walker, 1938; Fulton, 1943) although, on physiological and psychological grounds, their role in the higher mental organization of the individual is undoubtedly of the utmost importance (Penfield, 1946; Clark, 1948).

PHYSIOLOGICAL NEURONOGRAPHY.—Although not a histological technique, the method of physiological neuronography should be briefly mentioned. This technique (see McCulloch, 1944) depends upon the mapping out of large electrical potentials propagated as a result of the excitation of a local area of the brain by application of strychnine and has recently brought about advances in experimental neurology so remarkable that they have opened up a completely new approach to this field of study. However, in most cases, the anatomical basis for the nervous pathways along which these potentials travel still remains to be defined.

The results which have been obtained so far by the use of intravenous methylene blue on the central nervous system suggest that this method, if it is found to give consistently satisfactory results, may be a useful supplement to the experimental anatomical methods now available.

Material and Methods

Operation.—Young male and female rabbits weighing 1 to 1·5 kilogrammes were used in the present study. Enucleation of one eye was previously selected (Feindel and Allison, 1948) as a convenient control lesion for evaluating the staining method because the operative trauma is entirely extracranial and the anatomical features of the primary optic pathways are fairly well established (Clark, 1942; Fulton, 1943).

In each of eight animals one eye was removed under ether anæsthesia, with care to prevent traction on the optic nerve. Hæmostasis was secured by warm saline packs. Penicillin-sulphamezathine powder was then insufflated into the orbit and the lids closed by several interrupted silk sutures. The wounds were examined at autopsy and without exception were found to be free from infection and post-operative hæmorrhage. In two more animals, in addition to the removal of the eye, a unilateral olfactory tract section was made through an orbital approach. Normal brains from ten animals which were injected for the study of tissues other than the central nervous system were also available for comparative studies.

Injection of Dye.—At intervals varying from twenty-four hours to twenty days after operation the animals were lightly anæsthetized with intravenous nembutal (35 mg. per kg. of body weight) and given methylene blue (supplied by British Drug Houses Ltd.), in 0·9 per cent. physiological saline, by the intravenous drip technique previously described (Feindel, Sinclair, and Weddell, 1947).

However, in the present investigation, a more concentrated solution of the dye, up to 2·5 per cent., was used in order to decrease the volume of fluid injected and to obviate the risk of cerebral œdema. A large dose of the dye (300 to 500 mg. per kg. of body weight) was deliberately administered during the early experiments, but it is now clear that much smaller dosages may be adequate. The injection was regulated at 2 to 6 drops per minute, depending upon the concentration of the dye solution, and was usually prolonged for one to three hours. At the end of this time the animals were killed by a rapid overdose of a few c.cm. of the dye, or by an overdose of nembutal, or, in a few cases, by section of the medulla.

Histological Preparation.—The brain was then removed and immersed in a chilled solution of 6 per cent. ammonium molybdate, made up in 0·9 per cent. saline as suggested by the work of Cole (1946). Penetration of the molybdate into the brain tissue, which ensures uniform fixation of the dye, will occur to a depth of not much more than one centimetre. Sections of the brain were therefore cut at rather less than that thickness with a sharp razor blade, taking great care to

avoid distorting the tissue. Adequate fixation of the dye can be assured by keeping the tissue slices in the refrigerator at 0° to 2° C. for a period from two to sixteen hours, varying with the size of the specimen. After thorough washing in several changes of chilled saline (0·9 per cent.) for a period of fifteen to twenty minutes, the brain sections were kept in 10 per cent. neutral formol-saline for a period which, it was found, should not exceed three days. Frozen sections could then be cut and, after dehydration and clearing in xylol, mounted in neutral balsam.

Most of the tissue studied, however, was washed after formalin fixation and dehydrated in alcohol, using generous quantities and rapid changes to eliminate loss of dye. Some blocks were then cleared in xylol and embedded in paraffin, but it was later found that embedding by the double celloidin-paraffin method of Peterfi (see Romeis, 1924) gave superior preparations. The tissue blocks, when embedded, are a deep blue colour. They may then be sectioned and, without further staining, taken directly through xylol, alcohol and xylol, and mounted in neutral balsam.

The reagents most likely to dissolve out the stain are the ethyl alcohol and the solution of celloidin in methyl benzoate. The tissue blocks should be taken through these stages as rapidly as possible. Mounted sections, in spite of exposure to intense light for photographic purposes, are resistant to fading for many months.

Observations

Macroscopic Features

Staining of Normal Brain.—On removal of the calvarium the surface of the brain is usually pale blue but gradually darkens on exposure to air, until the entire brain appears deep blue in colour (Fig. 1). Some areas darken more rapidly than others, and in the early stages this gives a blotchy appearance to the cortex, with pale areas standing out, as for example, in the temporal poles of the brain illustrated in Fig. 2.

When the fresh brain is sliced, the "blueing" is seen to be confined to the external surface, although the cut surface soon becomes blue in turn. Adequate immersion in molybdate solution brings about a more even blueing of the dye throughout the entire block of tissue.

Grey matter is stained more deeply than white matter, so that normal fibre tracts, such as the corpus callosum and the internal capsule, remain pale (Fig. 3).

Staining of Degenerating Fibre Tracts.—Degenerating fibres take up the stain as intensely as grey matter and exhibit, in addition, a distinct purplish tinge. This deeper and metachromatic staining permits the ready identification of the degenerating optic nerve and outlines the bundle of crossed degenerating fibres in the optic tract (Figs. 1, 2, and 3). In the two instances in which an additional lesion in the olfactory tract was made, the definite purplish colour of the degenerating fibres provided sufficient contrast with the deep blue of the surrounding normal cortex to mark out by naked eye examination the distribution of olfactory fibres in the piriform area.

A further observation is that the differential staining of the degenerating fibres loses none of its distinctness as late as twenty days after removal of the eye (Figs. 2 and 3). Weddell and Glees (1941), injecting methylene blue locally, showed that degenerating fibres in cutaneous nerves are not stained by the dye later than fourteen days after experimental section. This difference may be due in part to the more rapid removal of degenerating neuronal products in the periphery, as compared to the central nervous system.

Microscopic Features.—The prepared sections of the brain have much the same appearance to the naked eye as sections stained by the ordinary Nissl technique. On microscopic examination the most outstanding features are the staining of the cell bodies and immediate processes of the neurons, the slight degree or absence of staining of normal fibre tracts in most regions, and the conspicuous differential staining of degenerating nerve fibres.

Nerve Cells and Inclusions.—Cytoarchitectonic differences in basal ganglia and cortical areas are sufficiently clear to allow their satisfactory identification, as, for example, the retrosplenial cortex shown in Fig. 9. Indeed, because there is some staining of matrix as well as cell bodies, differences between adjacent cell masses and layers are often more marked than in sections stained by the standard Nissl techniques (Fig. 29). Moreover, in many cases, satisfactory analytic staining of normal neurones clearly showing the finest ramifications of their axons and dendrites, as well as their nuclei, are obtained.

Usually the cytoplasm of neurones appears a homogeneous, clear, light pastel blue colour. In certain situations, however, a large number of fine blue granules are scattered throughout the perikaryon and along the axone, as shown in Figs. 27 and 28. In some cells there is superimposed upon this fine granulation a mass of coarse, dark-blue spherules, often inter-connected and closely packed about the nuclear region of the cell (Fig. 27).

The possible significance of these structures will be discussed below.

NORMAL NERVE FIBRES.—Normal nerve fibres are usually unstained but may occasionally be stained a green-blue colour. In some regions, for example the pons, the fibres show a smooth, evenly stained, wire-like appearance (Fig. 15), while in other areas, such as the internal capsule, they may sometimes present smooth ovoid varicosities (Fig. 16).

DEGENERATING FIBRES.—Degenerating fibres, on the other hand, are distinguished readily from normal fibres by their intense purplish shade of staining and by the morphological changes described below. These features render them conspicuous even under low-power magnification so that their main course and distribution may be rapidly traced in serial sections (Figs. 4, 5, and 10).

Under high magnifications, the degenerating fibres, with their purple staining (Figs. 7 and 8) and distorted outline (Figs. 11, 12, 13), are strikingly different from normal fibres (Fig. 15).

Characteristic Changes.—Many stages of fibre degeneration are present five days after the experimental lesion. The change in staining reaction probably takes place early, since many fibres with minimal distortion in outline have a distinct purple colour. This was suggested by studies in the peripheral nervous system where metachromasia occurs very soon after section of a cutaneous nerve (Weddell and Glees, 1941). Prominent varicosities appear at intervals along the swollen axis cylinders, and at a later stage these varicosities enlarge into round vesicular masses strung along the irregular swollen axones (Figs. 21, 22). The ballooned vesicles may reach an astonishing size and often appear hollow or reticulated (Figs. 12, 13). A characteristically blistered and purple axone is shown in Fig. 7. Finally, axones and vesicles lose their solid, densely stained appearance, become more lightly stained and mesh-like, and eventually disintegrate into coarse, irregular fragments. The vesicles often persist as isolated spherules with no apparent axonic thread connecting them (Fig. 13). Throughout all stages of degeneration the metachromatic staining is maintained, even for the fragments and granules of axones. It is of interest that these morphological changes in degenerating fibres as demonstrated by intravital methylene blue are almost identical with those described by Cajal (1928), who used the reduced silver nitrate technique, for many parts of the central nervous system including the primary optic pathway.

Site of Degeneration.—Five days after the lesion degenerative changes appear, in general, to be most advanced toward the termination of the optic tract, that is, in areas most remote from the lesion. This observation conforms with those obtained by Meader (1939), using the Marchi technique.

Fibre Sizes Affected.—Even making allowance for the degenerative changes, considerable variation of axone size is demonstrated in the optic tract. The degeneration at five days appears to affect the entire spectrum of fibre sizes, although it is more pronounced in the larger fibres. Some medium and small fibres may show granular fibrillated axones, sometimes without the formation of vesicles. But a number of individual fibres of the very finest diameter show ovoid swellings strung along an axone undergoing early fragmentation (See Figs. 6, 8, 11, 12, 13).

Again, in a general way, no sorting out of fibre sizes seems to occur at the level of the lateral geniculate body, and the fibres coursing on to the mid-brain are not necessarily those of the smallest diameter (Fig. 14). It is obviously necessary, however, for this observation to be substantiated by further study, particularly of material at shorter postoperative intervals and after minimal retinal lesions. The wide range of fibre size which is apparent in the material is illustrated in Figs. 6, 11, and 14 and no doubt provides a morphological basis for the differences of conduction velocity in the optic fibres which have recently been summarized by O'Leary (1944).

Fibre Bifurcation.—As in the peripheral nervous system, the intravenous methylene blue stains the individual degenerating axis cylinders. For this reason degenerating fibres may be traced for considerable distances. The precise course and direction of the axones are therefore readily determined (Figs. 6, 11). Collateral fibres are boldly outlined, for example, where they run towards the dorsal nucleus of the lateral geniculate body (Figs. 5, 11, 14), and the axone branching where these collaterals originate can usually be found (Figs. 10, 12, 14, 19, 20).

Node Formation.—At the site of axone branching a definite node-like formation may be seen, which often takes the form of a cuff placed just at the angle of the dividing axone (Figs. 19, 20), a picture very similar to that obtained by methylene blue and silver stains in the periphery. Constrictions may also be seen along the course of axis cylinders, and these too are suggestive of nodal structures (Fig. 17). It is of some interest, as Cajal (1928) observed with

silver stains, that swelling of the axoplasm during degeneration may first take place on either side of such a nodal constriction (Fig. 17). Further evidence for the existence of nodes in the central nervous system has been the presence at intervals along the purple degenerating axone of cuffs which are distinguished by their intense degree of staining and their green-blue coloration (Fig. 18). Although nodes on normal fibres in the central nervous system have been beautifully figured and described by Cajal (1911, 1928), for example, in the optic nerve and spinal cord, the present-day scepticism concerning their existence has prompted us to re-emphasize this finding in the light of the present observations (Allison and Feindel, 1948).

Degenerating Preterminals and Terminals.—The preterminal portions of the degenerating fibres, as well as the actual terminal *boutons*, may be stained both in the lateral geniculate body and in the midbrain. The preterminals may appear as strings of solid or vesicular beads among the ganglion cells upon which they terminate (Figs. 8 and 23). The normal terminals (Fig. 24) are small swellings which, at one level of focus under high magnification, appear as ring formations on the surface of the cells. Degenerating terminals take the form of enlarged solid plaques, which stain deeply with methylene blue (Figs. 25, 26). The appearance of the normal as well as the degenerating *boutons terminaux* corresponds closely to the picture obtained by the silver technique of Glees (Meyer and Meyer, 1945) or the double impregnation method of Hortega (Gibson, 1948). It has already been pointed out that the critical staining of such fine terminals by intravenous methylene blue may be related to the fact that the stain is applied to living nervous tissue (Feindel, Sinclair, and Weddell, 1947).

Non-nervous Structures.—Brief mention may be made of non-nervous structures stained by the same technique. Cerebral and intracerebral blood vessels are satisfactorily demonstrated. With heavy doses of dye, it is also possible to obtain staining of neuroglial elements. Thus the cell-bodies and processes of astrocytes, particularly in the region of small intracerebral blood vessels, may take up the dye. In addition, ependymal cells of the ventricular lining may stain selectively so that their unipolar processes can be seen extending into the cerebral tissue (Fig. 30).

Discussion

Previous Studies on Intravital Methylene Blue.—It should be noted that the general features of intravital methylene blue technique have by now become well established by numerous studies on the peripheral nervous system, which have been summarized by Dogiel (1926), Schabadasch (1935, 1936), and Weddell and others (1940). The fact that degenerating fibres in the periphery may be differentially stained by intravital methylene blue has been recognized for some time and utilized in a number of studies, including the innervation of the neuromuscular spindle (Hines and Tower, 1928), the origin of the fibres supplying Pacinian corpuscles in the mesentery (Sheehan, 1933), and the distribution and pattern of cutaneous nerve fibres and endings in experimental animals and man (Weddell, 1945). The early stages of degeneration in cutaneous nerve fibres have been studied in detail, using both vital methylene blue and silver methods, by Weddell and Glees (1941).

It is of historic interest that Ehrlich (1886), in his original paper on the use of methylene blue as a stain for living nerve tissue, described staining of nerve fibres in the medulla and cerebrum as well as pericellular networks of fine nerve fibrils in relation to cortical ganglion cells. Cajal (1911) placed great importance on methylene blue as an analytic stain for studies on the normal brain, and the many finely executed illustrations in his classic textbook indicate the remarkable success he achieved in applying the method. In his studies of nerve degeneration, in both the peripheral and central nervous systems, however, Cajal (1928) relied almost exclusively upon silver impregnations, dismissing the methylene blue method of Ehrlich because of his early observation (Cajal, 1896) that the results were uncertain and obtained only with difficulty. Reference to any other serious attempt to study fibre degeneration in the central nervous system by vital methylene blue has not been found (Feindel, 1948).

Advantages of the Intravenous Technique.—Many of the advantages and possible developments of the intravenous method which have been discussed with particular reference to the peripheral nervous system (Feindel, Sinclair, and Weddell, 1947) also apply to the technique as used for experimental studies on the central nervous system. Two main features are evident from the results described above. In the first place, almost the entire neurone —cell-body, cytoplasmic inclusions, axis cylinder, and terminals—may be demonstrated. Secondly, degenerating axones, preterminals, and terminals are conspicuously differentiated from normal axis cylinders.

Staining of Nerve Cells and Cellular Inclusions.—The staining of nerve cells as a

whole implies that the method may be developed as an analytic stain for normal central nervous tissue, serving to some extent as a substitute for the uncertain Golgi technique. Reference has already been made to Cajal's use of the method for this purpose, and similar brilliant results have been obtained more recently by Polyak (1941) in his well-known studies on the neuro-cytology of the retina. Many other structures of the normal neurone, such as the nodes of the axis cylinders and the peri-cellular terminals, are demonstrated.

The staining of granular inclusions within the cytoplasm of normal nerve cells, which show considerable resemblance in distribution and character to mitochondria and Golgi apparatus, is of some interest. Methylene blue has been used not only as a supravital stain for mitochondria and Golgi apparatus (Worley and Worley, 1943) but also as a stain for such intracellular substances as ribonucleoprotein (Wislocki and Dempsey, 1948). These observations suggest that the intravenous method, by virtue of being applied to living nervous tissue, may possibly be elaborated into a cytological technique for studying nerve cell inclusions. Since it is well known that cytoplasmic inclusions are intimately related to the metabolism and activity of the cell, the method may perhaps also be utilized as an indicator for the functional activity of different nerve cell groups. Indeed, Ehrlich (1885) was led at first to use methylene blue, not because of its histological value, but for indicating the level of metabolic gradients in different tissues of the living animal. Moreover, a number of most suggestive observations have been made on the pharmacological antagonism of intravital methylene blue and acetylcholine (see, for example, Cook, 1926) and it is not improbable that the vital staining of fine nervous terminals may be related to the high content of acetylcholine present in association with nerve endings (Nachmansohn, 1939). Further work along these lines is clearly indicated.

STAINING OF DEGENERATING FIBRES.—The ready identification of degenerating fibres by their metachromatic purple staining and by their characteristic vesiculation and swelling is also a feature of fundamental importance. The feasibility of identifying degenerating fibre tracts in macroscopic sections is of value in that it may provide an indication of the main areas to which a fibre system is distributed. Thus, it may serve as a useful complementary technique to silver methods, which are impractical for exploring very extensive regions of the brain. In microscopic sections, the individual degenerating axones can also be identified not only in their main course but even towards their terminations.

SIGNIFICANCE OF AXONE BRANCHING.—The method provides a means for noting axone bifurcation and for tracing collateral fibres, for example, where they sweep from the optic tract into the dorsal nucleus of the lateral geniculate body. The site and mode of axone branching in the central fibre tracts is a subject which has received remarkably little direct study, although it is a neural mechanism which may provide a great degree of flexibility for fixed anatomical pathways in the central nervous system. Thereby, functional connexions may be established by a single ganglion cell with different regions of the central nervous system which are widely separated.

The occurrence in the peripheral nervous system of such axone branching, which allows one nerve cell to have endings in two widely separated areas of skin, is implied by the work of Adrian and others (1931), and the significance of this axonal arrangement in providing an anatomical explanation of the mechanism of referred pain has recently been emphasized (Sinclair, Weddell, and Feindel, 1948).

Sherrington (1892) noted the incidence of geminal or bifurcating myelinated fibres in various parts of the brain and spinal cord. Cajal (1911) confirmed Nansen's classical studies on the division of dorsal root fibres in the spinal cord, and contributed observations of his own on fibre bifurcation in many regions of the brain stem and in the subcortical white matter. O'Leary (1944), with particular reference to the optic system, has recently described the influence which such axone branching may have on the character of electrical responses from central fibre tracts. In the present material, extensive axone division appears to take place at the level of the lateral geniculate body, with some branches coursing towards the dorsal nucleus (Figs. 5, 10, 11, 14) and others running on towards midbrain nuclei. In both regions many axones, before their final termination, also frequently show branching (Figs. 19, 20). Cajal (1911) by the use of Ehrlich's methylene blue method in the rabbit, found axone bifurcation in a small number of fibres in the optic chiasm, one branch passing backwards into each optic tract.

Fibre branching of this nature is obviously of relevance in anatomical studies of the visual pathway, for example, in the determination of the ratio of retinal ganglion cells to optic fibres. Furthermore, such a mechanism may provide an actual anatomical basis for a number of phenomena related to the bilateral representation of the visual pathways, such as macular sparing, which have heretofore been unsatisfactorily explained.

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Like the Marchi technique, it gives a highly contrasting picture of the main course of degenerating fibre tracts. It has the additional advantage, which the silver techniques possess, of staining the degenerating axis cylinder independently of the presence of a myelin sheath, so that non-myelinated as well as myelinated fibres may be traced. Again, as in the silver method, the preterminals and terminals, particularly the degenerating *boutons terminaux*, are demonstrated in relation to the cell bodies of the neurones, thus permitting a precise definition of the terminal distribution of the fibres. Unlike the silver impregnation, however, where the degenerating fibres must often be differentiated by careful observations from a rich background of neuropil, the methylene blue fortunately has an affinity for degenerating fibres while it stains normal fibres only to a slight degree or not at all. This enables the distribution of a smaller number of degenerating fibres to be recognized much more quickly over an extensive topographical area than can be done by the use of silver stains. The method may therefore be applicable to the study of diffusely arranged or sparsely constituted fibre pathways. Moreover, the staining and technical preparation of the material is likely to be less arduous than with the impregnation methods, and, unlike the latter techniques, which must be carried out on frozen sections, the material stained with intravital methylene blue may be embedded and sectioned serially in the ordinary way.

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Further Development of the Method

IMPROVEMENT OF TECHNIQUE.—At present the successful preparation of material depends upon three essential points: (1) the slow perfusion of sufficient dye into the animal to produce staining of the central nervous system; (2) the uniform oxidation and fixation of the dye; and (3) the histological fixation of the tissue itself. Since further investigations on these points are still in progress, only brief mention will be made of them.

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perfusion of concentrated solutions of methylene blue into the pregnant animal has given distinct staining of embryos in rabbits and guinea-pigs (Feindel, 1948). This aspect of the technique may prove of considerable value in neuroembryological studies.

Summary

The possible applications of intravenous methylene blue for experimental studies on the central nervous system are considered. The method offers the advantage of staining most parts of the normal neurone—cell-body, inclusions, axis cylinder, and terminals—and gives in addition a differential staining of degenerating axones, preterminals, and terminals. The site and mode of axone bifurcation can be readily studied, and the significance of this, particularly in the optic system, is discussed. Nodal structures on axones in the central nervous system are clearly demonstrated. The technique is compared to the other methods available for studying degeneration in the central nervous system. A few developments of the method, including its use for neuroembryological studies, are outlined.

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REFERENCES

Adrian, E. D., Cattell, McK., and Hoagland, H. (1931). *J. Physiol.*, **72,** 377.
Allison, A. C., and Feindel, W. H. (1948). (In the press).
Bethe, A. (1895). *Archiv. mikr. Anat.*, **44,** 579.
Brodal, A. (1940). *Arch. Neurol. Psychiat. Chicago*, **43,** 46.
——(1948). *J. Comp. Neurol.*, **88,** 157.
Clark, W. E. Le Gros (1932). *Brain*, **55,** 406.
——(1942). *Physiol. Rev.*, **22,** 205.
——(1945). "The Tissues of the Body." 2nd Edit. Oxford University Press.
——(1948). *Lancet*, **2,** 353.
——, and Penman, G. G. (1934). *Proc. roy. Soc.*, **114B,** 291.
——, and Meyer, M. (1948). *Brain*, **70,** 304.
Cole, E. C. (1946). *Stain Tech.*, **21,** 63.
Cook, R. P. (1926). *J. Physiol.*, **62,** 160.
Dogiel, A. S. (1926). In "Enzyklædie der Mikroskopischen Technik," R. Krause. Third Edit. Berlin. Urban and Schwarzenburg. pp. 1390–1414.
Ehrlich, P. (1885). *Zbl. med. Wissenschaft*, **23,** 113.
——(1886). *Biol. Zbl.*, **6,** 214.
Feindel, W. H. (1948). "A Study of Neural Patterns by the Aid of Intravital Methylene Blue." D.Phil. Thesis. University of Oxford.
Feindel, W. H., and Allison, A. C. (1948). *Science*, **107,** 429.
——, Sinclair, D. C., and Weddell, G. (1947). *Brain*. **70,** 495.
——, ——, ——(1948). *Nature*, **161,** 318.
——, Weddell, G., and Sinclair, D. C. (1948). *J. Neurol. Neurosurg. Psychiat.*, **11,** 113.
Fulton, J. F. (1943). "Physiology of the Nervous System." Second Edit. New York and London. Oxford University Press.
Gibson, W. C. (1937). "McClung's Handbook of Microscopical Technique." Second Edit. London. Oxford University Press. pp. 481–488.
——(1948). (Personal communication.)
Glees, P. (1943). *Brain*, **66,** 229.
——(1944). *J. Anat.*, **78,** 47.
——(1946). *J. Neuropath. and exp. Neurol.*, **5,** 54.
——, and Clark, W. E. Le Gros (1941). *J. Anat.*, **75,** 295.
Goldmann, E. F. (1909). *Beit. z. klin. Chir.*, **64,** 192.
Häggqvist, G. (1936). *Z. mikr-anat. Forsch.*, **39,** 1.
Heller, R. E., Thomas, R. W., and Davenport, H. A. (1947). *Stain Technol.*, **22,** 111.
Hines, M., and Tower, S. (1928). *Johns. Hopk. Hosp. Bull.*, **42,** 264.
Hinshaw, G. R., Feindel, W. H., and Weddell, G. (1948). In preparation.
Hoff, E. C. (1935). *Arch. Neurol. Psychiat. Chicago*, **33,** 687.
Lassek, A. M., and Rasmussen, G. L. (1939). *Arch. Neurol. Psychiat., Chicago*, **42,** 872.
McCulloch, W. S. (1944). "The Precentral Motor Cortex." Ed. Paul Bucy. Urbana, Ill., University of Illinois Press. Chapter 8.
Marchi, V. and Algeri, G. (1885). *Riv. sper. freniat.*, **11,** 492.
Meader, R. G. (1939). *Proc. Koninklijke Nederland Akad. Wettenschappen.*, **42,** 1.
Mettler, F. A. (1932). *Stain Technol.*, **7,** 95.
Meyer, A., Beck, E., and McLardy, T. (1947). *Brain*, **70,** 18.
——, and Meyer, M. (1945). *J. Anat.*, **79,** 180.
——, and Crawford, J. (1948). *Brain* (In the press).
Millen, J. W. (1948). *J. Anat.*, **82,** 68.
Minckler, J. (1942). *Amer. J. Path.*, **18,** 1061.
Minkowski, M. (1920). *Schweiz. Arch. Neurol. Psych.*, **6,** 201.
Nachmansohn, D. (1939). *J. Physiol.*, **95,** 29.
Nissl, F. (1892). *Allg. Z. Psychiat.*, **48,** 197.
O'Leary, J. L. (1944). "The Precentral Motor Cortex," ed. Paul Bucy, Urbana, Illinois. University of Illinois Press. Chapter 3.
Penfield, W. (1946) *Brit. med. J.*, **2,** 639.
Phalen, G. S., and Davenport, H. A. (1937). *J. Comp. Neurol.*, **68,** 67.
Polyak, S. L. (1941). "The Retina." Chicago. University of Chicago Press.
Ramón y Cajal, S. (1896). *Rev. trim. micrograf.*, **1,** 26.
——(1911). "Histologie du Système Nerveux de l'Homme et des Vertébrés." Paris. A. Maloine. 2 vols.
——(1928). "Degeneration and Regeneration of the Nervous System." London. Oxford University Press. 2 vols.
Romeis, B. (1924). "Taschenbuch der Mikroskopischen Technik." Eleventh Edit. Munich and Berlin. R. Oldenbourg.
Schabadasch, A. (1935). "Theoretische und experimentelle Studien zur Methylenblaufärburg des Nervengewebes." Gorkij. Staatsverlag.
——(1936). *Bull. d'Histol. Appl.*, **13,** 5 ; 72 ; 137.

Sheehan, D. (1933). *J. Anat.*, **67**, 233.
Sherrington, C. S. (1892). *J. Physiol.*, **13**, xxi.
Sinclair, D. S., Weddell, G., and Feindel, W. H. (1948). *Brain*, **71**, 184.
Swank, R. L., and Davenport, H. A. (1934). *Stain Technol.*, **9**, 129.
——(1935). *Ibid.*, **10**, 87.
Walker, A. E. (1936). *J. comp. Neurol.*, **64**, 1.
——(1938). "The Primate Thalamus." Chicago. University of Chicago Press.
Weddell, G. (1945). *Brit. med. Bull.*, **3**, 167.
——, and Glees, P. (1941). *J. Anat.*, **76**, 65.
——, Harpman, J. A., Lambley, D. G., and Young, L. (1940). *J. Anat.*, **74**, 255.
Wislocki, G. B. (1920). *Contr. to Embryol.* (Carnegie Inst.). **11**, 45.
——(1921). *Ibid.*, **13**, 91.
——, and Dempsey, E. W. (1948). *J. comp. Neurol.*, **88**, 319.
Worley, L. G., and Worley, E. K. (1943). *J. Morph.*, **73**, 365.

(FOR ILLUSTRATIONS SEE PAGES 239–242 INCLUSIVE, AND COLOUR INSET. DESCRIPTIONS OF THE ILLUSTRATIONS APPEAR ON PAGE 238.)

All illustrations are of brains of rabbits injected intravenously with methylene blue. Except where otherwise noted, illustrations of microscopic sections are of material showing degeneration five days after removal of one eye.

PLATE I.

FIG. 1.—Whole brain shortly after removal showing the type of staining obtained. The right eye was removed ten days previously. Note darker staining of right optic nerve. (Approximately ⅔ natural size.)

FIG. 2.—Enlarged view of optic chiasm, showing darker staining of right optic nerve and left optic tract twenty days after removal of right eye. (Approximately × 2.)

FIG. 3.—Cross-section of another fresh brain twenty days after removal of right eye, showing darker purplish staining of right optic nerve. Note the pale staining of the left optic nerve and the white matter. (Approximately × 2.)

FIG. 4.—Region of lateral geniculate body as seen in microscopic section, showing staining of degenerating fibres five days after removal of contralateral eye. (× 25.)

FIG. 5.—The same section, at higher magnification, showing collateral fibres running at right angles toward the dorsal nucleus of the lateral geniculate body (represented at the lower right of the illustration). (× 150.)

FIG. 6.—Another region of the same section showing the variation in size of the degenerating optic tract fibres. (× 250.)

FIG. 7.—A single degenerating fibre, showing the blistering and purple staining of the axon. (× 550.)

FIG. 8.—Degenerating preterminal fibres and nerve-cells in the midbrain. Note the intense purplish staining of the fibres as contrasted to the green-blue of the nerve cells. (× 550.)

PLATE II.

FIG. 9.—Cerebral cortex, retrosplenial area, showing typical staining of nerve cells. (× 80.)

FIG. 10.—Region of lateral geniculate body showing degeneration of crossed optic fibres. Note, at upper left, collaterals coursing toward dorsal nucleus at right angles to main fibres. At lower right, a Y-shaped bifurcation may be made out. (× 75.)

FIG. 11.—Detail from Fig. 10, showing main optic fibres and collaterals. (× 450.)

PLATE III.

FIG. 12.—Degenerating fibres and terminals in the dorsal nucleus of the lateral geniculate body of the side opposite to the lesion. The vesiculation and early fragmentation of the fibres is to be noted. (× 625.)

FIG. 13.—Details of degenerating fibres in another part of the lateral geniculate body in the same case. Note the irregularity and swelling of fibres and the isolated axonic balls. (× 625.)

PLATE IV.

FIG. 14.—Crossed degenerating fibres in the optic tract skirting the dorsal lateral geniculate nucleus. Note collaterals leaving the tract at right angles to pass into the nucleus, and fibres of both large and small size continuing onward. (× 550.)

FIG. 15.—Normal fibres in the pons. Note the smooth outline and uniform staining. Such fibres are also stained green-blue, rather than purple as are degenerating fibres. (× 550.)

FIG. 16.—Apparently normal fibres in the internal capsule which show slight varicose thickenings but do not show the metachromasia of degeneration. (× 550.)

FIG. 17.—Detail showing optic tract fibres of different size, both of which have nodal constrictions. The swelling in the smaller fibre appears most marked on either side of the constriction. (× 1,100.)

FIG. 18.—Deeply stained node on a degenerating fibre in the brachium of the superior colliculus four days after enucleation of the contralateral eye. (× 1,250.)

FIG. 19.—Fibre bifurcation in the optic tract, showing deeply stained nodal cuff at the site of branching. (× 1,100.)

FIG. 20.—Degenerating fibre in the pretectum, showing the typical dark cuff at the site of bifurcation. (× 1,100.)

FIG. 21.—Detail of degeneration in fine fibre. (× 1,100.)

FIG. 22.—Detail in large degenerating fibre. (× 1,100.)

PLATE V.

FIG. 23.—Pretectum, showing disintegration of fine fibres and preterminals amongst the cells of the pretectal nucleus. (× 550.) (Compare with Fig. 8.)

FIG. 24.—Normal terminal ring on a nerve cell of the large-cell nucleus of the optic tract. (× 1,250.)

FIG. 25.—Enlarged and deeply stained terminal plaques on a nerve cell of the large-cell nucleus of the optic tract four days after enucleation of the opposite eye. (× 1,250.)

FIG. 26.—Enlarged terminal *boutons* on a ganglion cell in the dorsal nucleus of the lateral geniculate body on the side opposite to the lesion. (× 1,250.)

FIG. 27.—Pontine cell, showing coarse perinuclear material as well as fine granulation throughout the cytoplasm. (× 1,000.)

FIG. 28.—Nerve cells of the frontal cortex, showing fine cytoplasmic granulation. (× 1,000.)

FIG. 29.—Cells and fibres of the pons, showing staining of neuropil. (× 65.)

FIG. 30.—Ependymal cells of the lining of the third ventricle. (× 625.)

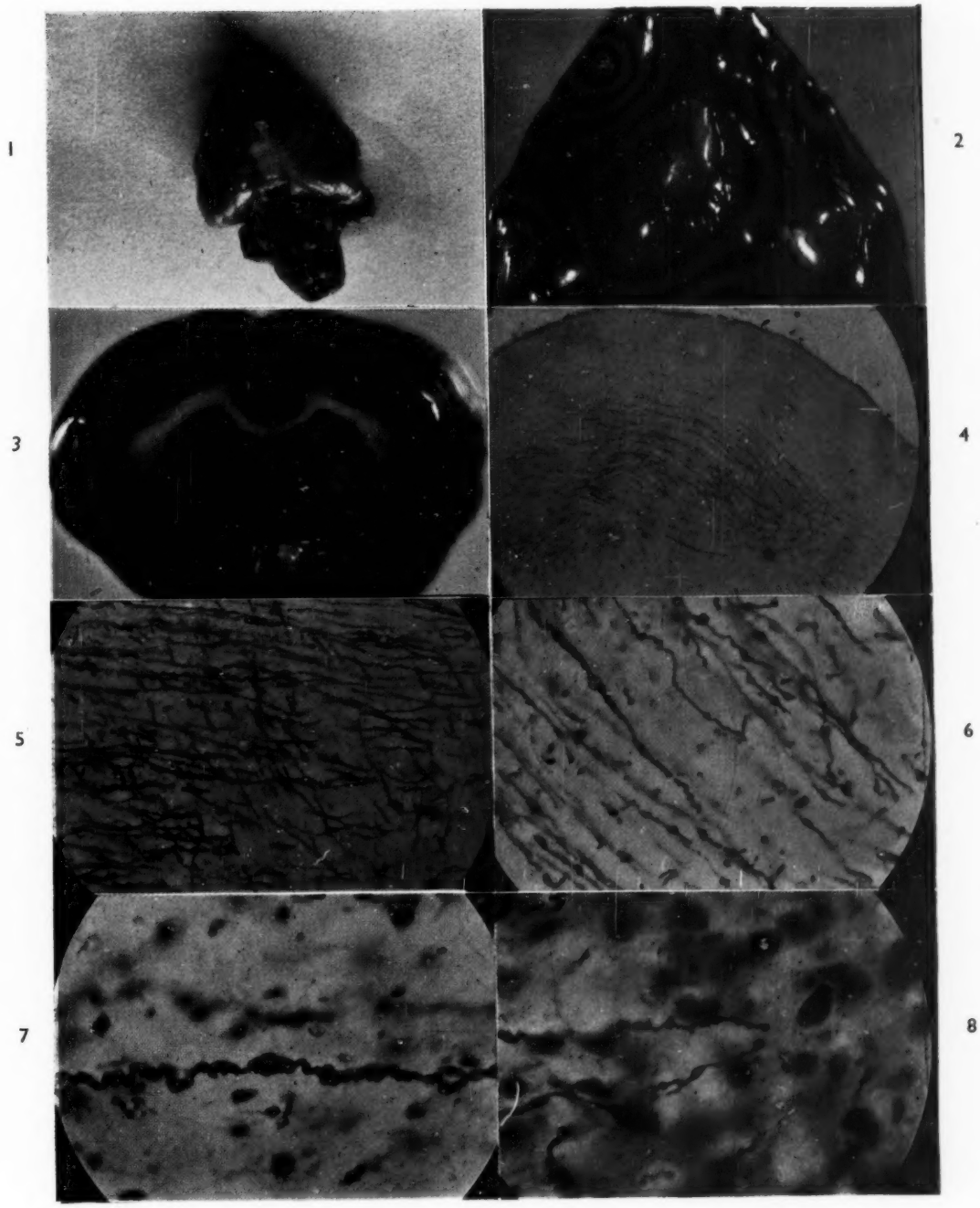

PLATE I.

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[*Facing page* 238

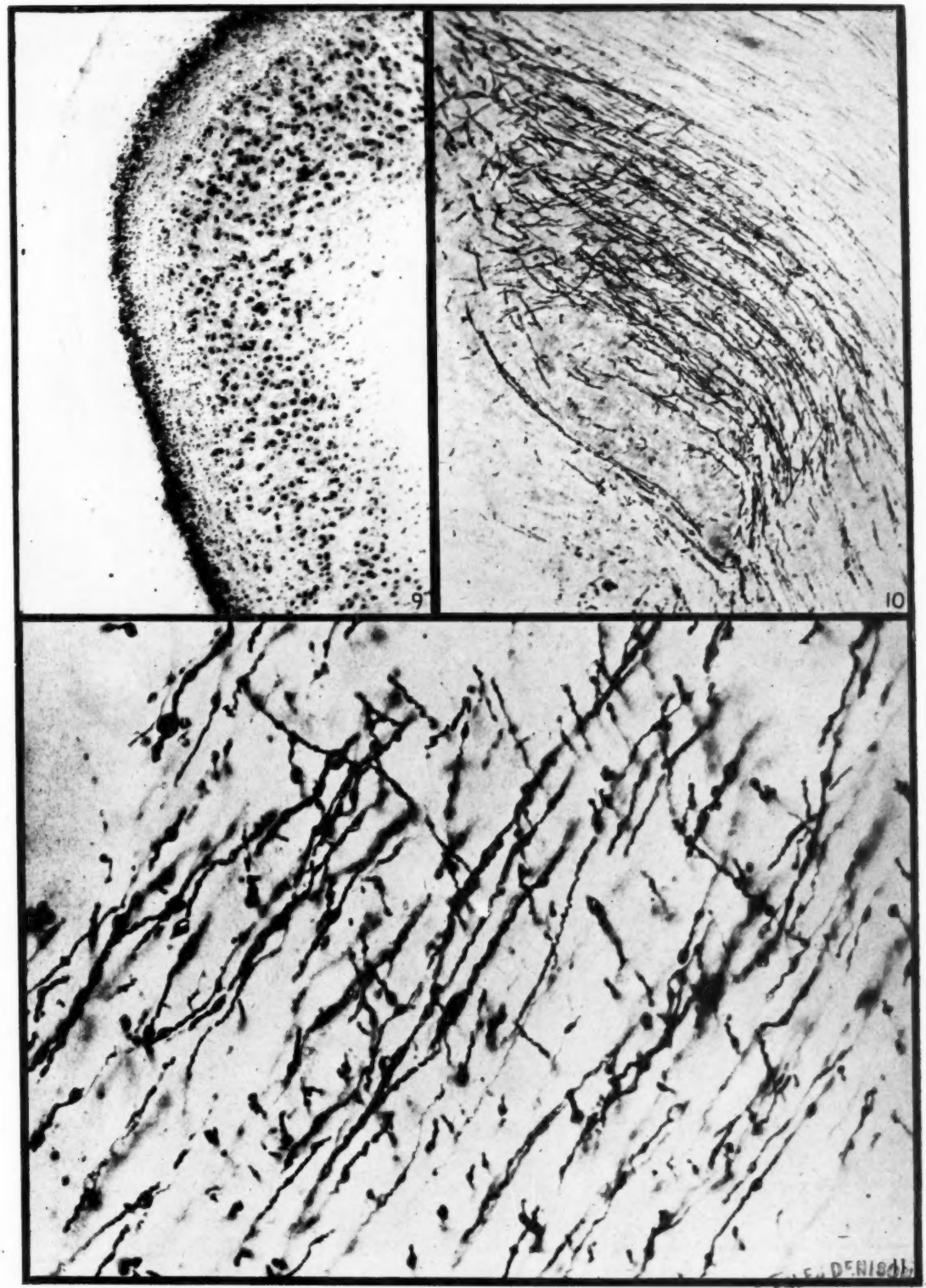

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PLATE II.

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PLATE III.

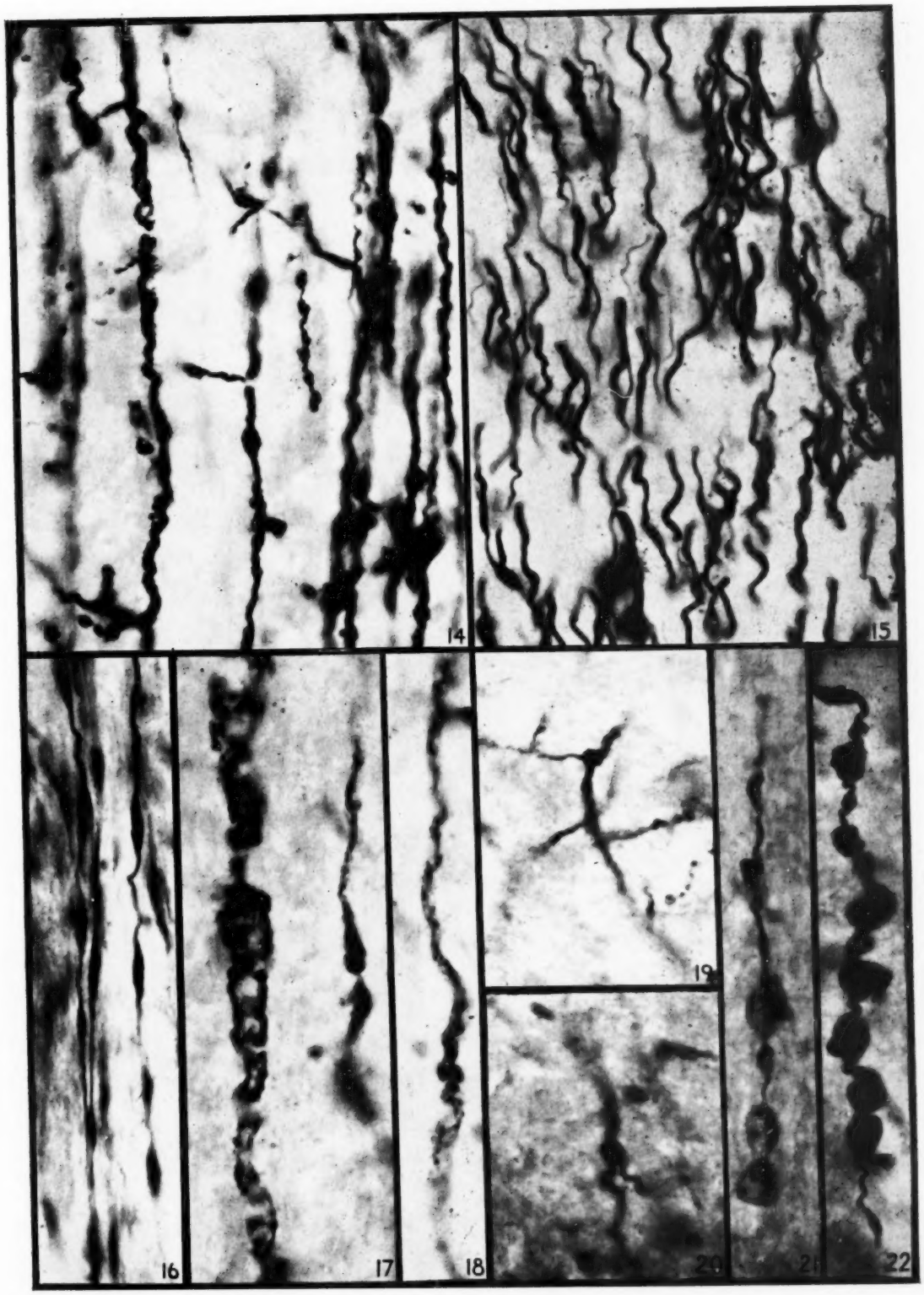

PLATE IV.

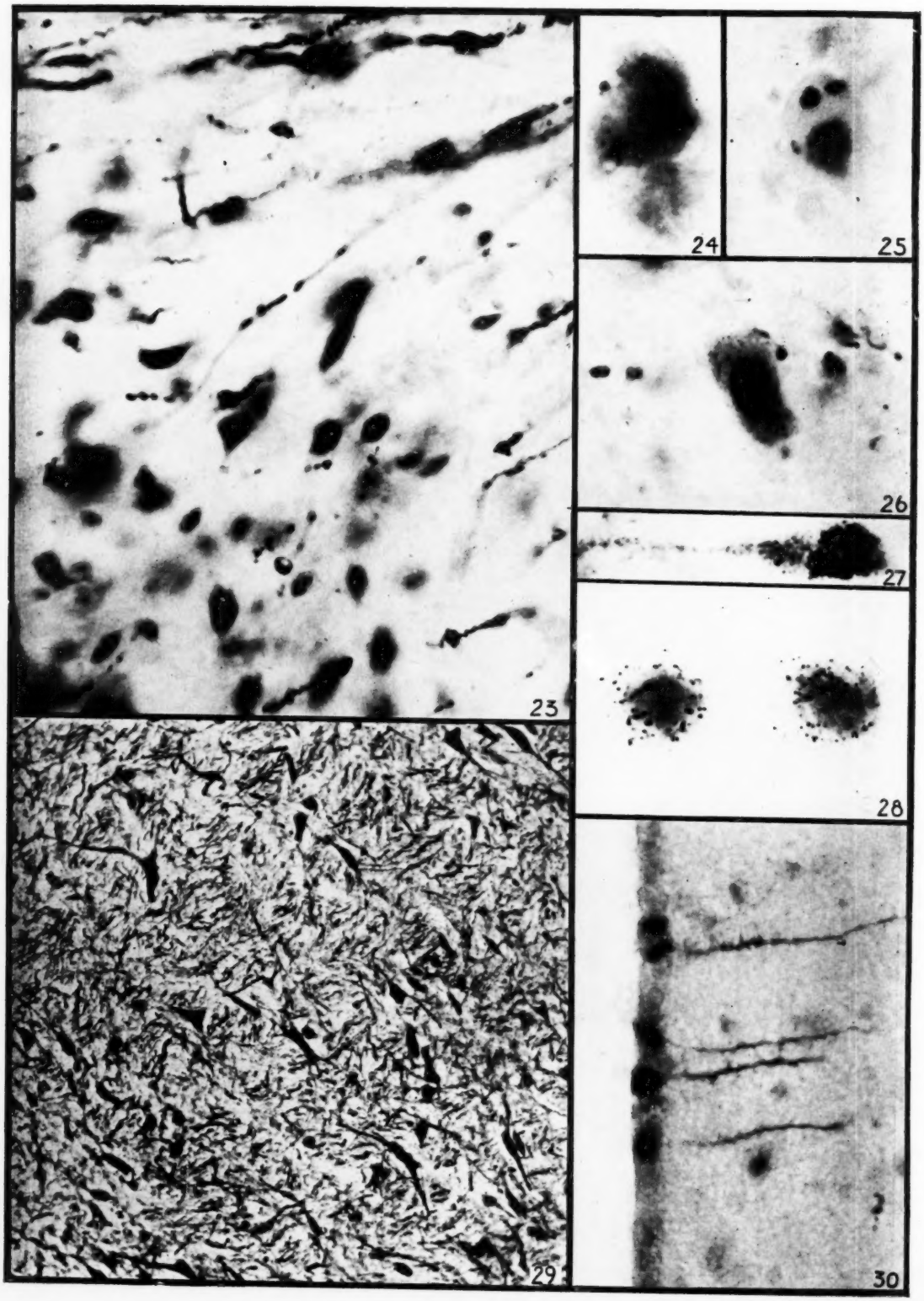

PLATE V.

NEUROVASCULAR RELATIONS AND ANOMALIES AT THE BASE OF THE BRAIN

BY

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(RECEIVED JUNE 10, 1948)

A knowledge of neurovascular relations and anomalies at the base of the brain is of importance both for an understanding of certain obscure cranial nerve palsies accompanying diseased vascular states or expanding intracranial lesions, and for an appreciation of cranial nerve topography for the purposes of intracranial surgery. The object of this paper is to direct attention to some normal anatomical features which appear to have been neglected and to record certain anomalous arrangements of a highly practical character which have not hitherto been described.

The observations are based on an examination of the brains of 210 dissecting-room subjects in which the anatomical relations at the base of the brain were studied during and following their removal from the cranial cavity. An advantage of this material was that all the brains were hardened *in situ*, so that the configuration of the parts was preserved.

Clinical records of the cases examined were unfortunately rarely available so that it was not possible to correlate the anatomical findings with any ante-mortem symptomatology where signs of nerve compression might have been expected. The author is aware that this considerably limits the scope of the present study, since in themselves the observations advance no conclusive evidence that the neurovascular relations of the type here described were, or are, responsible for nerve palsies. There is, on the contrary, abundant evidence that nerves may be grossly stretched, compressed, and deformed without the development of any signs or symptoms of disordered function. All that is claimed is that these observations demonstrate that, even when the normal arrangement obtains, large arteries are on occasion so related to nerves that they may press upon, displace, and deform them. In this way they could conceivably impair their function. This possibility is further increased by the presence in some cases of certain anomalous arrangements, and in others, where the vessels are the subject of atheromatous changes or are abnormally large, tortuous, or pulsating. There is already a voluminous literature relating to the association between intracranial aneurysms and the signs and symptoms of nerve compression (Peacock, 1876 ; Beadles, 1907 ; Fearnsides, 1916 ; Symonds, 1923 ; Jefferson, 1937 ; Dandy, 1944 ; and others). The present report, however, is not concerned with the excursions and possible effects of such arterial lesions.

Observations

The Optic Nerve

The internal carotid, ophthalmic, and anterior cerebral arteries are in contact with the optic nerve between the optic chiasma and the optic foramen.

On perforating the roof of the cavernous sinus between the anterior and middle clinoid processes the internal carotid artery is applied against the infero-lateral surface of the optic nerve. The artery then winds outwards beneath the nerve to reach the angle at the lateral extremity of the chiasma between the diverging optic nerve and optic tract, where it gives its terminal branches. The artery is thus directly applied to the infero-lateral and lateral aspects of the optic nerve at its chiasmal extremity.

Below the nerve the carotid artery gives the ophthalmic branch, which runs to the optic foramen infero-lateral to and in contact with the nerve. The anterior cerebral artery arises in the angle referred to and passes medially above the nerve to reach the longitudinal fissure. The optic nerve is thus directed laterally between, and may be compressed by, the anterior cerebral artery above and the internal carotid artery below.

These vessels are all favourably disposed to exert direct pressure on the optic nerve, and when this occurs the quadrants first involved will be determined by the neurovascular relations. The vessel

usually responsible is the internal carotid artery. In Fig. 1 is shown a specimen in which an atheromatous right internal carotid artery compressed the optic nerve and the adjacent surface of the brain while following an unusually tortuous course after its departure from the cavernous sinus.

Partial optic atrophy caused by the pressure of an atheromatous internal carotid or opthalmic artery has been described on several occasions (Elliot Smith, 1905 ; Fuchs, 1924 ; Traquair, 1938).

The Oculomotor Nerve

On emerging from the medial sulcus of the cerebral peduncle, the oculomotor nerve is directed forwards and outwards across the interval outlined by the midbrain posteriorly, the dorsum sellæ anteriorly, and the free margin of the tentorium laterally. The nerve skirts the lateral margin of the posterior clinoid process, which it occasionally grooves, and then passes on to the dural roof of the cavernous sinus along which it continues for some distance before finally penetrating the dura and reaching the lateral wall of the sinus. The site of entry into the dura is usually midway between the anterior and posterior clinoid processes. The nerve consequently runs an exposed course not only while crossing the hiatus of the tentorium but also on the dural roof of the sinus, against the firm surface of which it may be compressed.

At the brain stem the nerve is wedged in the angle outlined between the posterior cerebral and superior cerebellar arteries where these emerge from the terminal portion of the basilar artery. The former branch is directed outwards and slightly upwards over the nerve and above the free margin of the tentorium, while the latter continues laterally beneath the nerve and the tentorium. The angle outlined by these diverging vessels varies in degree, but occasionally it is so narrow that the nerve is constricted where it passes between them. When the basilar artery divides at a lower level than usual the posterior cerebral artery is directed more steeply upwards and outwards in order to clear the free margin of the tentorium, and, in crossing the nerve, may drag on it (Fig. 2). Windle (1888) reported a specimen in which a branch of the posterior cerebral artery pierced the nerve.

Between the posterior and anterior clinoid processes the nerve is closely related to the internal carotid artery. The nerve first crosses the vessel while coursing forwards and outwards across the dural roof of the sinus, which separates it from the artery, and then reaches the lateral wall of the sinus in which, now lateral to the artery, it continues forward to enter the superior orbital fissure. If its entry into the sinus wall is delayed the nerve may be compressed against the roof by the artery as the latter leaves the sinus and turns backwards and outwards to reach the angle between the optic nerve and tract. Involvement of the oculomotor nerve in aneurysmal swellings of the sinus portion of the artery is well known.

The posterior communicating artery usually courses medial to the nerve as it runs between the internal carotid and posterior cerebral arteries. When this vessel is enlarged and replaces the posterior cerebral it is often situated further laterally and so may come to overlie the oculomotor nerve, which is then interposed between it and the firm dural roof of the sinus. Fig. 3 illustrates the grooving of the nerve consequent on such an arrangement. Fig. 4 is of another specimen in which both the internal carotid and posterior cerebral arteries were resting on, and compressing, the nerve before its entry into the sinus wall.

The calibre of the arteries forming the circle of Willis was measured in a hundred specimens. The measurements revealed that the posterior cerebral artery took origin predominantly or entirely from the internal carotid artery on both sides in 6 per cent., and on the right and on the left in 13 per cent. of the specimens respectively (Table I). The corresponding figures of Windle (1888), De Vriese (1904), Fawcett and Blachford (1906), Blackburn (1907), and Stopford (1915) are included for purposes of comparison.

Table I

Calibre of Arteries Forming the Circle of Willis

	Both Sides %	Right %	Left %
Windle (1888)	2	5	4
De Vriese (1904)	—	20	8
Fawcett and Blachford (1906) ..	—	1	1
Blackburn (1907)	10	7	5
Stopford (1915)	2	5	3
Sunderland (this investigation)	6	13	13

An atheromatous and markedly curved basilar artery arched upwards and to the right in two specimens to reach the under surface of the oculomotor nerve, which it elevated and displaced laterally (Fig. 5).

The Trochlear Nerve

Though the trochlear is a thin nerve and runs a long course from the tegmentum of the midbrain to the cavernous sinus, it is nevertheless well protected throughout the greater part of its course by the free margin of the tentorium, beneath which

it runs as far as its entry into the sinus (Fig. 6). It is thereby shielded from the posterior cerebral artery and the associated supratentorial structures. Inferiorly, however, the nerve is interposed between the tentorium and the superior cerebellar artery. Though the nerve is directed between the posterior cerebral and superior cerebellar arteries, it cannot be constricted between them since, in contradistinction to the arrangement in the case of the oculomotor nerve, the firm tentorium is interposed between them. An aneurysm on the superior cerebellar artery could, however, compress the nerve against the tentorium.

The Trigeminal Nerve

The relations of the trigeminal nerve and its three divisions in the lateral wall of the cavernous sinus to the internal carotid artery are too well known to require description.

Attention is directed to a vein, which was almost invariably present, which passed from the inner end of the great horizontal fissure of the cerebellum to the inner end of the superior petrosal sinus immediately lateral to the trigeminal nerve.

Usually a small transverse pontine branch of the basilar artery runs laterally beneath the root of the nerve at the pons. This vessel was never so large as to indent the nerve, though its position should be noted in surgical procedures on the nerve root. Stopford (1915) and Watt and McKillop (1935) have described this branch.

As the superior cerebellar artery passes to the cerebellum it frequently loops downwards to the upper surface of the trigeminal nerve. The vessel may indent the nerve (Fig. 7, two specimens) or perforate it (Fig. 8, one specimen).

In three specimens (right 2, left 1) the posterior inferior cerebellar artery reached, and grooved, the under surface of the nerve root after looping upwards ventral to the pons, the facial and auditory nerves, and the anterior inferior cerebellar artery (Fig. 9).

In two specimens an abnormally elongated and curved basilar artery arched to the left to reach and compress the inner margin of the sensory root (Fig. 10).

The most interesting and unusual of the anomalous arrangements observed affecting this nerve and also the abducent (see later) was one in which a large anastomotic channel ran from the basilar artery to join the internal carotid artery in the cavernous sinus. The first specimen observed formed the subject of a report in 1941 (Sunderland) since which time two additional specimens have been examined —making a total of three in 210 specimens. The arrangement in two of the specimens is illustrated in Figs. 11 and 12 : the one description suffices for all three. The anastomotic channel, which was left-sided in each case, left the basilar artery at the level of the trigeminal nerve roots and coursed laterally, dorsal to the abducent nerve, till it reached a position posterior to the upper margin of the apex of the petrous temporal and immediately medial to the sensory root of the trigeminal nerve. In two specimens the vessel then accompanied the nerve through the trigeminal foramen into Meckel's Cave, while in the third the artery entered the cavernous sinus through a separate foramen to reach the carotid artery.

Where the nerve and the artery crossed the apex of the petrous temporal together the latter was in direct contact with, and slightly grooved, the flattened upper surface of the sensory root over its inner aspect. In Meckel's Cave the vessel arched downwards, internal to the Gasserian ganglion, turned medially, pierced the inner dural wall of the Cave, and entered the cavernous sinus. It then joined the lateral aspect of the internal carotid artery just after that vessel had entered the sinus.

The anastomotic channel was, in each specimen, the largest branch of the basilar artery and twice the diameter of the posterior cerebral arteries. In all three specimens the remaining branches of the basilar and the formation and branches of the Circle of Willis were normal in size and arrangement. In one specimen both vertebral arteries were threadlike, and in the other two the vertebral on the side of the anomaly was considerably reduced in size. The anastomotic channel presumably functioned as a compensatory mechanism for the reduced size of the vertebral arteries.

Anomalous anastomoses between the internal carotid and basilar arteries have been reported by Quain (1844), Tüngel (1860), Duret (two, 1874), Tareniecki (1880), Flesch (1882), Hochstetter (two, 1885), Decker (1886), Batujeff (1889), Elliot Smith (1909), and Oertel (1922). In Batujeff's case the basilar artery took origin from the left carotid artery at the base of the skull and entered the posterior cranial fossa through the anterior condyloid foramen. In the other cases the aberrant vessel branched from the internal carotid artery in the cavernous sinus and passed posteriorly either through (Quain, Tüngel, Tareniecki, Hochstetter (two), Oertel) or around (Duret (two), Flesch, Decker, Elliot Smith), the dorsum sellæ to reach the basilar artery. The condition was present on the right side in the cases described by Hochstetter (one), Tareniecki, Tüngel, Duret (two), and Oertel, and on the left in the remainder. In the cases described by Elliot Smith, Decker, and Flesch the anastomotic vessel, while in the cavernous sinus,

was related to the Gasserian ganglion and its branches. Their cases, however, differed from those described here in that the vessel skirted the lateral margin of the dorsum sellæ to enter the posterior cranial fossa, and did not bear the same intimate relationship to the sensory root of the trigeminal nerve.

Such anastomoses are probably established in the following manner. In the embryo many small anastomotic channels linking the internal carotid and vertebral arterial systems develop at the base of the brain and subsequently transfer their origin from the internal carotids to the basilar artery—the latter having been outlined previously by the fusion of the cranial extremities of the vertebral vessels. As a relic of this embryonic relationship, it is not unusual to see the posterior cerebral artery taking origin from the internal carotid after that vessel has emerged from the cavernous sinus. The anomaly under discussion represents the persistence of one of the early anastomotic channels which are usually absorbed as development proceeds.

This vascular anomaly owes its importance to the close relationship which the anastomosing vessel bears to the sensory root and Gasserian ganglion of the trigeminal nerve—a relationship so intimate as to leave an impression on the nerve root. Dandy (1939) believes that pressure on the sensory root by a branch of the basilar artery is responsible, in the majority of cases, for the pain in tic douloureux. In two of these cases there was evidence that the vessel had exerted pressure on the nerve root, and this pressure, moreover, must certainly have been greatly increased by the pulsations occurring in a vessel of the size present. An investigation of the past history in one case revealed no record of any disturbance of trigeminal nerve function. Case records were not available for the other two.

The Abducent Nerve

The abducent nerve passes upwards, forwards and slightly outwards from the ponto-medullary junction, just lateral to the mid-line, to the wall of the inferior petrosal sinus. It enters and accompanies the latter beneath the petro-clinoid ligament to the cavernous sinus, along which it continues to the superior orbital fissure.

The nerve is related at the brain stem to the anterior inferior cerebellar, basilar and vertebral arteries and in the sinus to the internal carotid artery.

Anterior Inferior Cerebellar Artery.—The relations of the anterior inferior cerebellar artery to the nerve are summarized in Table II. The artery was anterior to the nerve on the right in 84 per cent. and on the left in 73 per cent. of the specimens. These figures closely parallel those of Stopford (1915), who reported figures of 86 per cent. and 81 per cent. respectively.

In three specimens, all on the left side, this vessel passed through the nerve (Fig. 10). This anomaly has been reported by Valenti (1 specimen), Cushing (3 specimens, 1911) and Stopford (2 specimens, 1915) and in each case it was on the left side. Watt and McKillop (1935) described an artery posterior to the nerves in 40 per cent. and one anterior in 78 per cent. of the sixty specimens examined by them.

On sixteen occasions in the present series the artery deeply grooved the nerve on crossing ventral to it. The past histories were traced in six of these cases and from them it seemed certain that no squint or diplopia had been present during life.

In 1910 Cushing advanced the view that obscure abducent palsies accompanying expanding intracranial lesions could, in certain cases, be explained on the basis of a strangulation of these nerves by the anterior inferior cerebellar arteries. This view was supported by a mass of carefully collected and analysed data in which he showed "(1) that the arteries, contrary to the usual anatomical description, generally overlie the nerves; (2) that in a series of brains of tumour cases the vessels which normally encircle the brain stem often produce a more or less deep grooving of the nervous tissues; (3) that the abducentes in many of these cases are deeply constricted and (4) that a large percentage of the clinical histories of cases which show post-mortem pontine grooving, with accompanying implication of the nerves, record either subjective diplopia or the actual presence of a convergent squint observed during life." In conclusion he emphasized the need for an investigation of a larger series of brains than the pathological ones he had examined in order to confirm the neurovascular relations observed by him.

The results of the present investigation and those reported by Stopford (1915) amply confirm Cushing's observations. Stopford, however, believed that "when the artery lies in the dorsal position, the abducent nerve may be compressed against the basi-sphenoid by the vessel, as the former structure proceeds towards the cavernous sinus." My observations support Cushing's contention that the nerve is compressed when the artery is running anterior, and not posterior to it. There is some evidence, however, to suggest that this grooving is not uncommon and is not necessarily associated with signs and symptoms of disordered conduction in the nerve.

Collier (1904) had previously attributed these

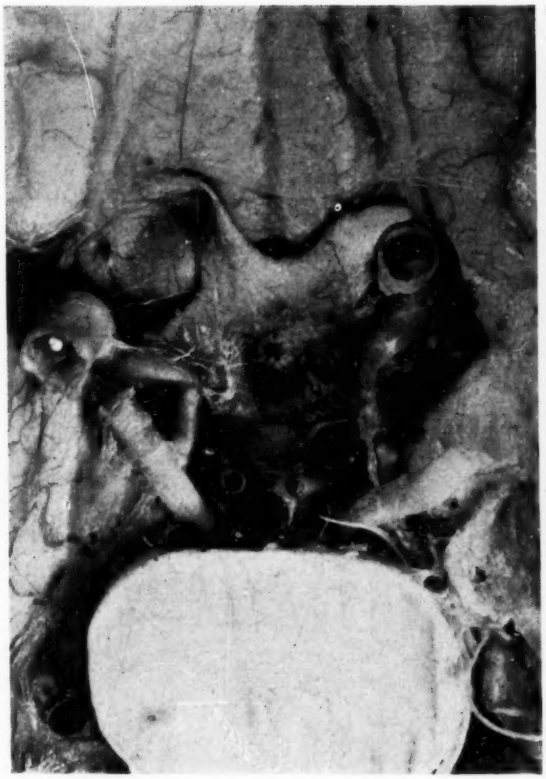
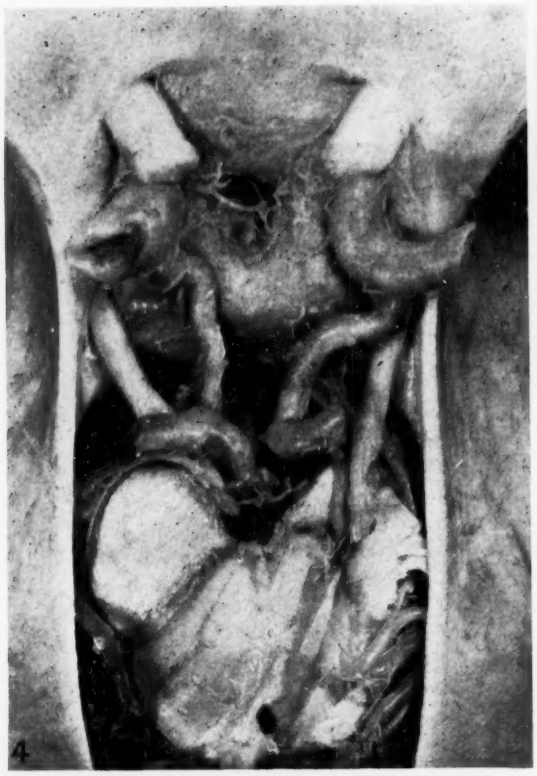


FIG. 1.—Chiasmal region of the base of the brain, showing the right internal carotid artery compressing the right optic nerve and the adjacent surface of the brain.

FIG. 2.—The base of the skull in the region about the pituitary fossa, the cavernous sinus, and the interval between the brain stem and dorsum sellæ (from above). The posterior cerebral artery has been removed on the left side, exposing a deep groove extending into the upper surface of the third nerve. The groove was caused by the artery as it crossed and dragged on the nerve.

FIG. 3.—The base of the skull in the region about the pituitary fossa and cavernous sinus (from above). The left posterior cerebral artery, which branched from the internal carotid artery, has been removed thereby revealing the groove outlined by it on the upper surface of the oculomotor nerve.



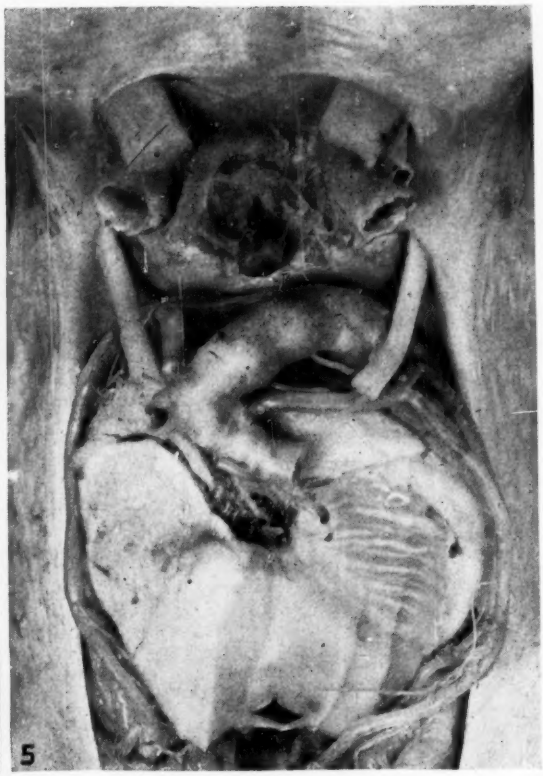
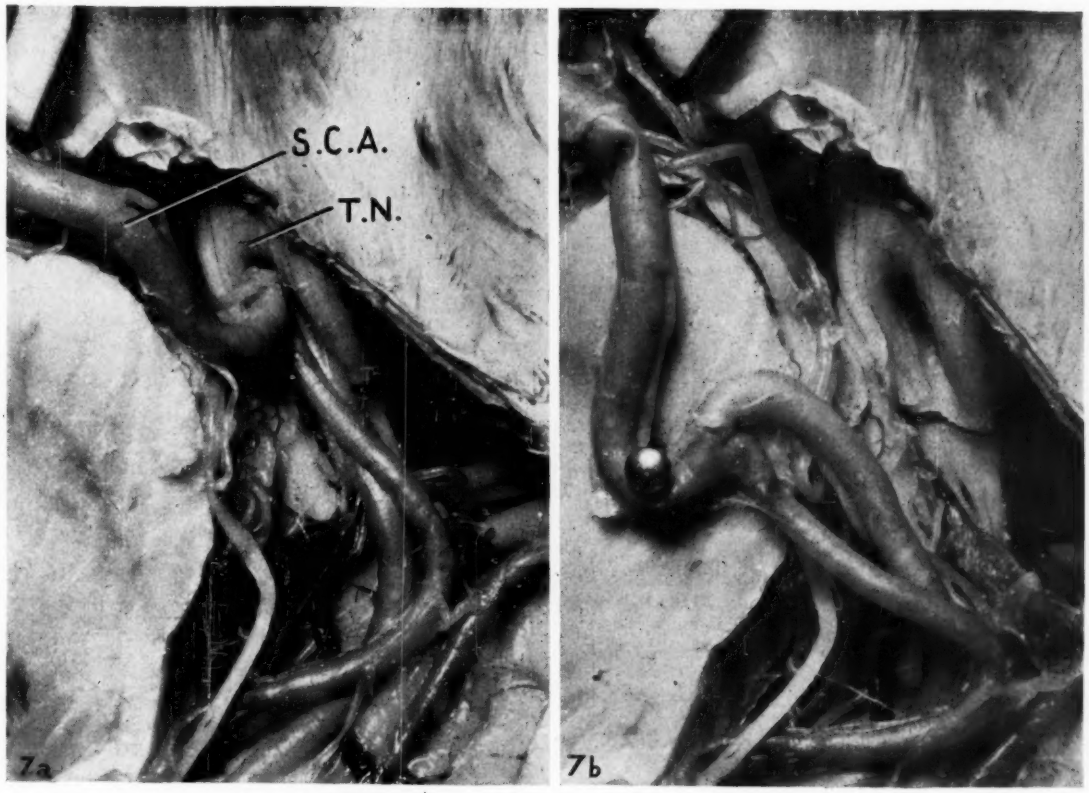


FIG. 4.—The base of the skull in the region about the pituitary fossa, the cavernous sinus, and the interval between the brain stem and dorsum sellæ (from above). The right internal carotid artery and the posterior cerebral artery arising from it are shown pressing on the oculomotor nerve where that structure is coursing on the roof of the sinus preparatory to entering it.

FIG. 5.—The interval (from above) between the brain stem and dorsum sellæ, showing the basilar artery arching upwards to displace the right oculomotor nerve upwards and to the right.

FIG. 6.—A dissection (from below) of the hiatus of the tentorium and its contents. The protected course pursued by the trochlear nerve beneath the margin of the tentorium is shown.



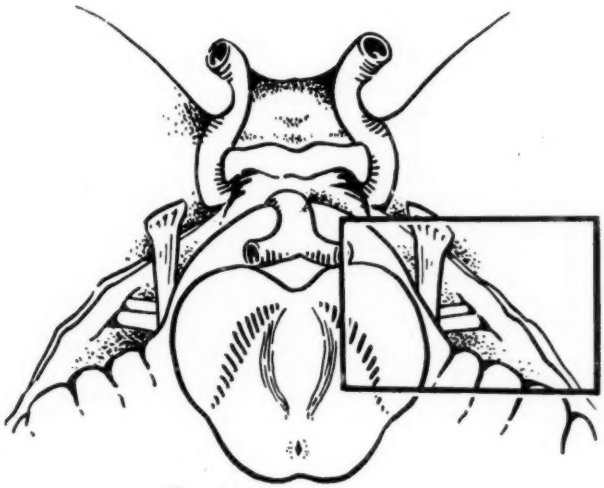
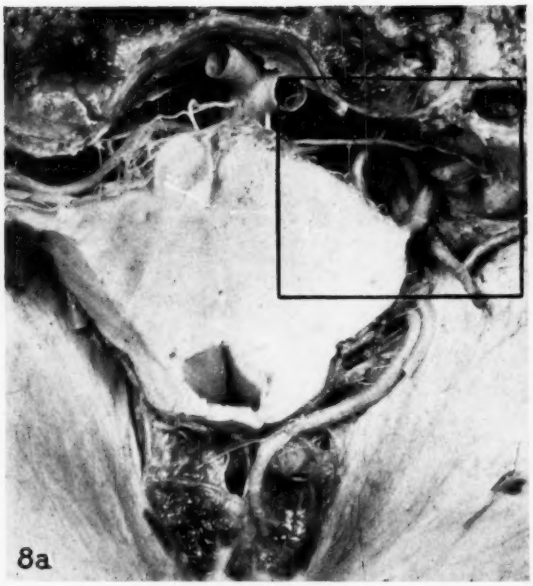
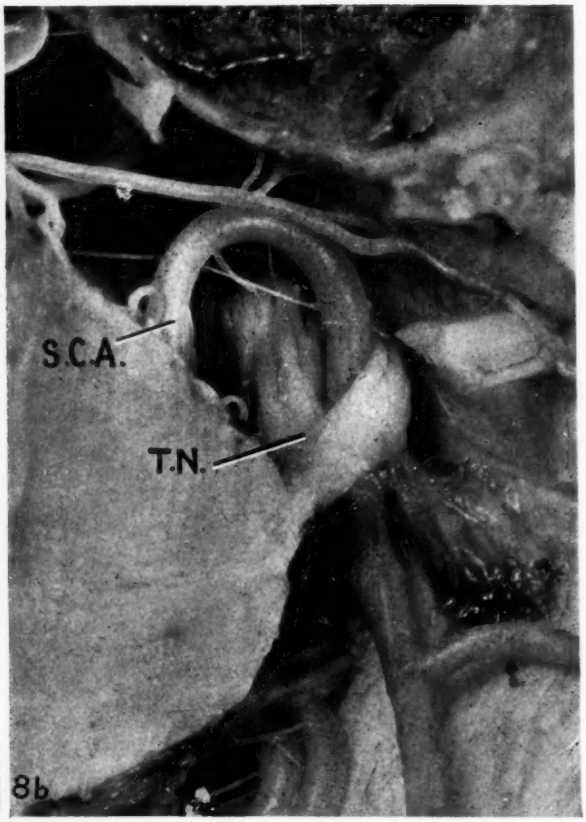


FIG. 7.—The right cerebellopontine angle (from above) following the removal of the tentorium. (*a*) The superior cerebellar artery (S.C.A.) is shown indenting the sensory root of the trigeminal nerve (T.N.). (*b*) The artery has been reflected and the depression in the nerve root exposed. (*c*) The region under consideration.





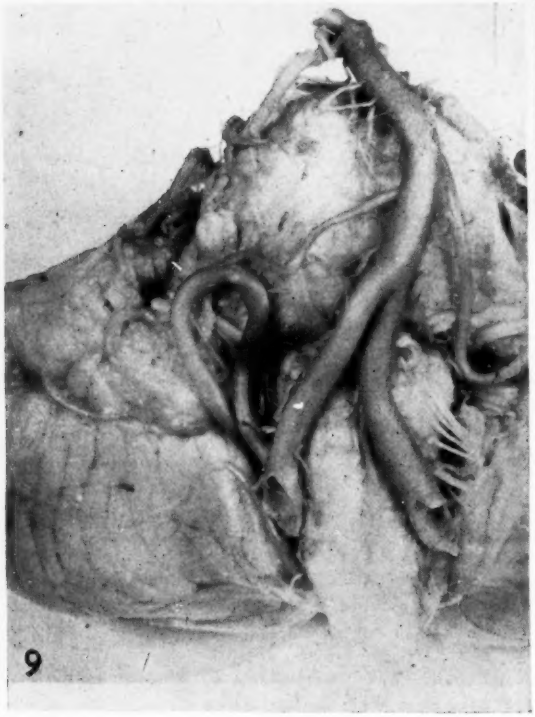


FIG. 8.—A dissection (from below) of the posterior cranial fossa. The trigeminal nerve (T.N.) has been exposed from below by removing the cerebellum and transecting the brain stem at the pons. The superior cerebellar artery (S.C.A.) is shown passing through the sensory root of the nerve.

FIG. 9.—The ventral surface of the brain stem and cerebellum. The right posterior inferior cerebellar artery is shown looping upwards ventral to the facial and auditory nerves to reach and impress the sensory root of the trigeminal nerve.

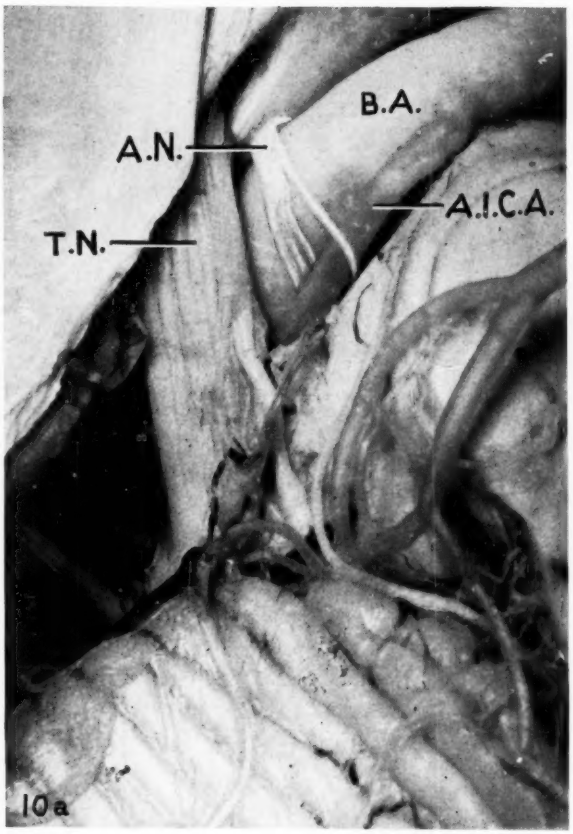


FIG. 10.—(*a*) The left cerebellopontine angle (from above) following the removal of the tentorium. The trigeminal nerve (T.N.) is shown coursing forwards from the pons to the trigeminal foramen. The basilar artery (B.A.) is shown arching upwards and to the left and impinging on the under surface of the nerve root. The abducent nerve (A.N.) is also shown curving over the vessel while the anterior inferior cerebellar artery (A.I.C.A.), which has been drawn upwards with the basilar artery, is passing through the abducent nerve. The ventral aspect of the brain stem in this specimen is shown in Fig. 13, in which the arrow is directed to the sixth nerve at the site where it is turning over the basilar artery. (*b*) The region under consideration.

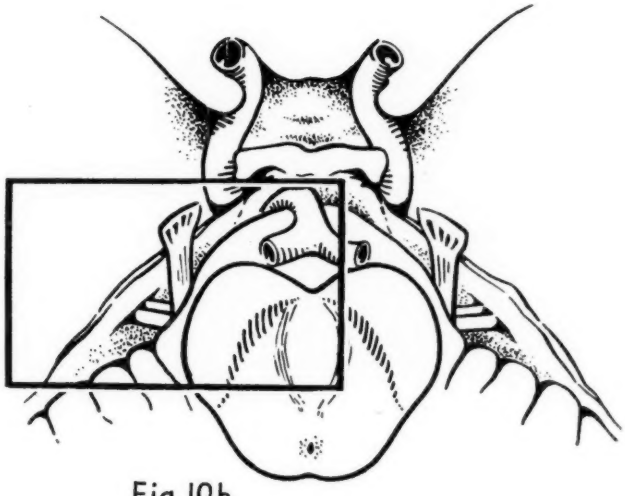


Fig. 10b

FIG. 11.—Photograph taken through the hiatus tentorii cerebelli, the left margin of which has been divided and displaced, to show the course taken by the anomalous vessel in the posterior cranial fossa. The terminal portion of the basilar artery is seen in the centre of the field and posterior to it the divided surface of the pons, which is partly obscured by the curved right margin of the hiatus. The relationship of the anomalous vessel to the sensory root of the trigeminal nerve, as these structures cross the apex of the petrous temporal to enter Meckel's Cave, is well shown.

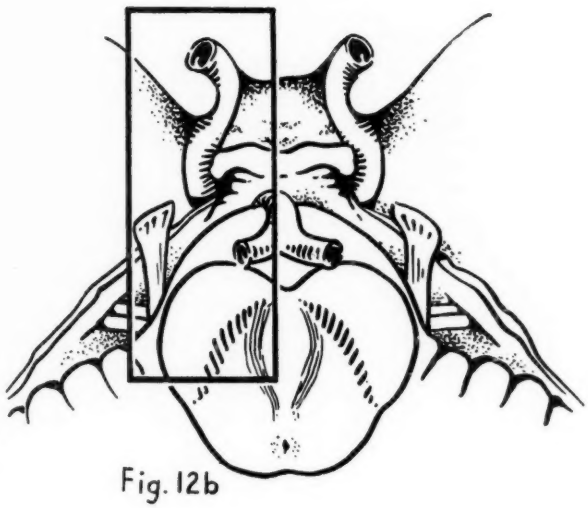


FIG. 12.—(*a*) A dissection (from above) of the contents of the cavernous sinus and the structures related to the upper surface of the apex of the petrous temporal. The sensory root of the trigeminal nerve (T.N.) is shown passing forwards. Immediately to its medial side is the large anastomotic channel (A.A.) from the basilar artery, which can be seen joining the internal carotid artery (I.C.A.) in the cavernous sinus. The abducent nerve (A.N.) is entering the sinus medial to the anastomotic vessel, and when the latter turns down to join the carotid artery the nerve is directed laterally anterior to it. The looping of the internal carotid artery referred to takes the vessel upwards into a position which corresponds to that occupied by the anastomotic channel just after it has entered the sinus. The course of the nerve relative to the loop corresponds with the arrangement illustrated here. (*b*) The region under consideration.

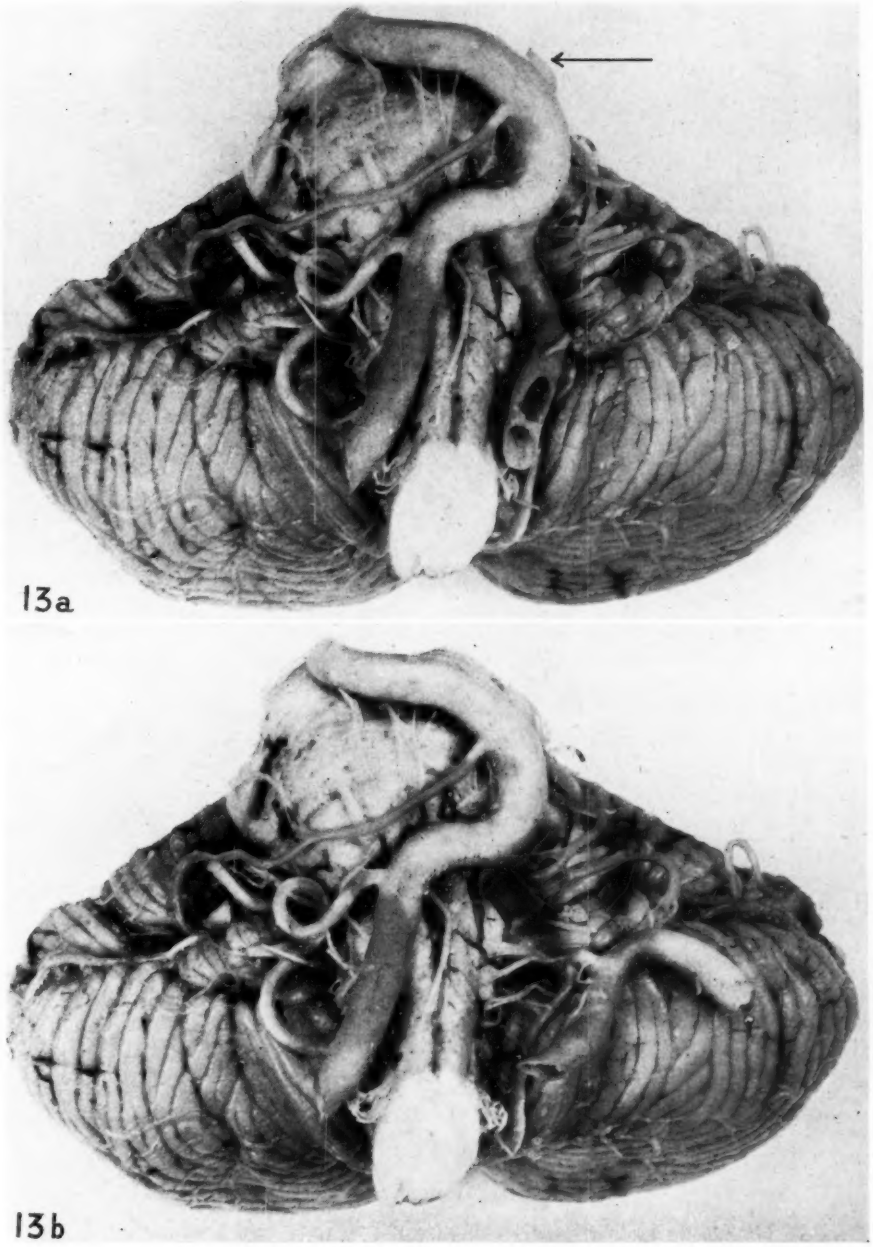
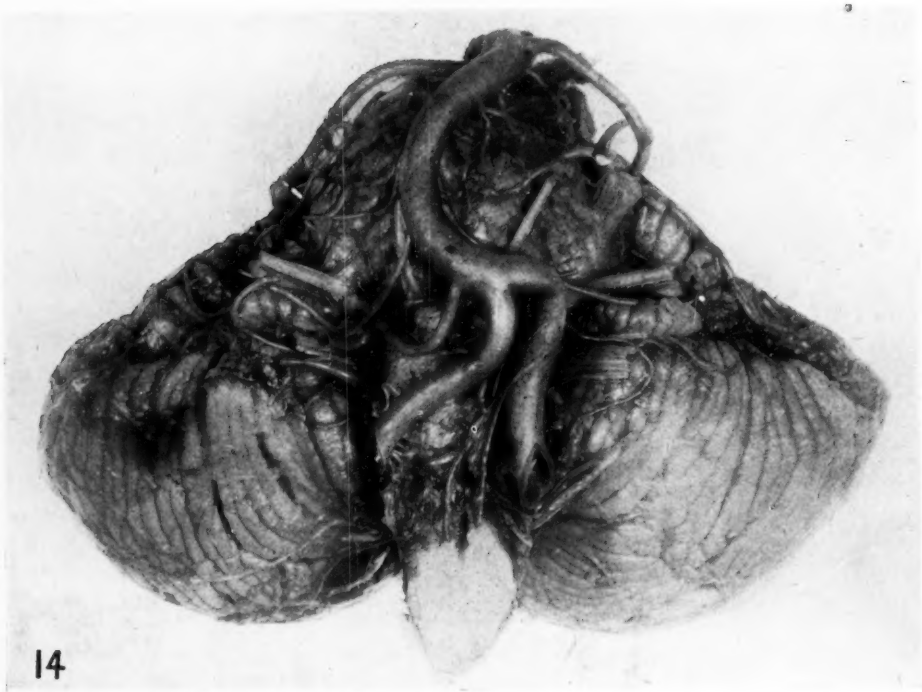
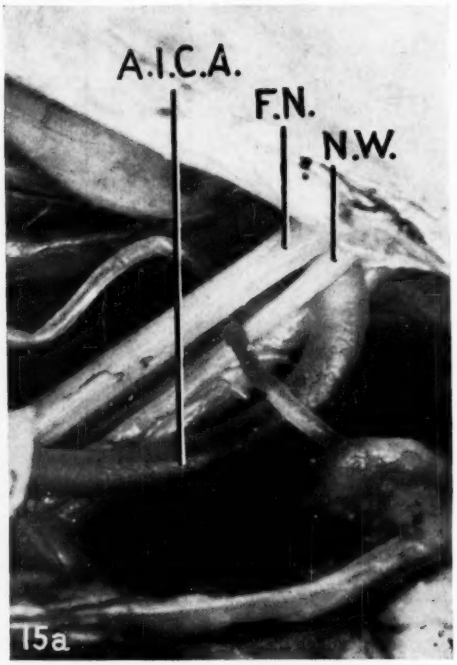


FIG. 13.—Photographs of the ventral aspect of the brain stem and cerebellum showing : (1) the basilar artery arching to the left anterior to the abducent nerve, which can be seen emerging from behind and turning over the artery ; (2) the left vertebral artery arching backwards into the interval between the cerebellum and medulla and compressing the glossopharyngeal, vagus, and accessory rootlets. The depression caused by the artery is shown in Fig. 13b.





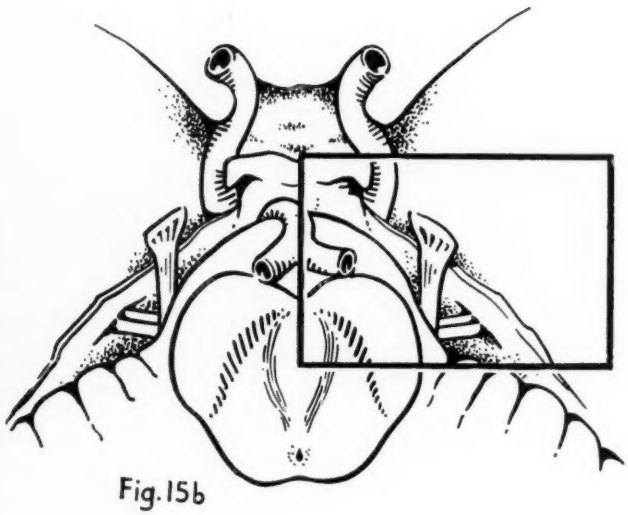


FIG. 14.—The ventral surface of the brain stem and cerebellum showing the left vertebral artery sweeping anterior to the abducent, facial, and auditory nerves and compressing them against the pons.

FIG. 15.—(*a*) The right cerebellopontine angle has been exposed from above after the tentorium has been reflected and the cerebellum displaced inwards and backwards. The facial (F.N.) and auditory nerves and the nervus intermedius of Wrisberg (N.W.) are shown passing to the internal auditory meatus. The loop of the anterior inferior cerebellar artery (A.I.C.A.) is shown presenting into the mouth of the canal after having been withdrawn from it when the cerebellum was displaced. The returning limb of the arterial loop is seen passing between the facial nerve and the nervus intermedius above and the auditory nerve below. (*b*) The region under consideration.

palsies of the abducent nerves to the displacement " backwards " of the brain stem from supratentorial pressure which, in the initial stages, produces traction on the nerves, first on the involved side and then on the other. Wolff (1928) claimed that if this were the factor responsible then the frailer trochlear nerve, with its long antero-posterior course, should be the first nerve affected. However, the direction of the displacement inferred in Collier's description is downwards and not antero-posteriorly as interpreted by Wolff

According to Wolff (1928) the factor responsible for the involvement of this nerve is the bend which it takes over the apex of the petrous temporal as it enters the cavernous sinus, so that the nerve is kinked and constricted at this point when the brain stem is driven downwards. In this connexion it should be noted that the first two points of fixation along the course of the nerve are at the ponto-medullary junction and at the site where the nerve pierces the dura in relation to the inferior petrosal sinus. Consequently, displacement of the brain stem downwards would, in the initial stages, be more likely to stretch the nerve between these two points. The author is convinced, from an anatomical investigation of the disposition of the parts, that Collier's explanation is the more acceptable though in certain cases the neurovascular arrangement, as described by Cushing and confirmed by Stopford and this study, may operate in the manner originally suggested by Cushing.

Internal Auditory Artery.—The internal auditory artery was not significantly related to the abducent nerve in any specimen.

Basilar Artery.—Occasionally (Table III) the basilar artery is deviated to one or other side of the mid-line and comes to overlie directly the abducent nerve, thereby compressing it against the pons. In one specimen the vessel was so curved as to compress both nerves. The greater tendency of the basilar artery to shift or bend to the left (Dandy, 1944) was confirmed in this series.

In four specimens a markedly curved basilar artery swung to the left and displaced the nerve laterally. In two of these the artery curved so far laterally that it projected beneath the nerve and forced it upwards as high as the upper margin of the pons. The nerve first ascended vertically, compressed against the pons and then turned over the vessel and descended to reach the site where it pierced the dura in relation to the inferior petrosal sinus. The nerve was, in this manner, acutely angulated over the artery between its origin and the point where it entered the dura (Figs. 10 and 13).

Vertebral Arteries.—In approximately 17 per cent. of the specimens one or other or both vertebral arteries curved ventral to, and compressed, the nerve at the ponto-medullary junction (Fig. 14). The arrangement obtaining in these specimens together with the incidence on the two sides is shown in Table III.

Internal Carotid Artery.—The abducent nerve enters the cavernous sinus above the level of the carotid artery as that vessel enters through the floor. The nerve then proceeds along the lateral aspect of the artery and leaves the sinus at the superior orbital fissure. The artery frequently runs a tortuous, rather than a gently curved, course in the sinus and on two occasions, both on the left side, was observed looping acutely upwards immediately on entering the sinus so that the loop ascended lateral to the entering abducent nerve. This necessitated the latter curving abruptly round the front face of the loop in order to reach the lateral aspect of the vessel. The arrangement was similar to that illustrated in Fig. 12.

The Anastomotic Channel between the Internal Carotid and Basilar Arteries.—The anastomotic channel linking the internal carotid and basilar arteries (described above) bore a constant relation to the abducent nerve in the three specimens observed. The nerve entered the cavernous sinus medial to the channel and then, where this vessel turned down to unite with the carotid, curved abruptly ventral to it in order to cross the carotid and reach its supero-lateral aspect along which it continued (Fig. 12).

The Facial and Auditory Nerves

Anterior Inferior Cerebellar Artery.—The anterior inferior cerebellar artery is usually intimately related to the facial and auditory nerves at the ponto-medullary junction, in the cerebello-pontine angle, and at or in the internal auditory meatus. The results of an investigation of the relations of the vessel to these nerves in 132 subjects, with special reference to the internal auditory meatus, have been the subject of an earlier report (Sunderland, 1945).

In 39 per cent. of the specimens the artery passed outwards, anterior to the facial and auditory nerves, to enter the meatus down which it looped for a variable distance. Before passing to the cerebellum the recurrent limb of the loop then coursed between, above, or below the nerves, either in the meatus or soon after leaving it (Fig. 15).

In 25 per cent. of the specimens the artery just reached the entrance of the meatus into which the apex of the loop projected ventro-medial to the nerves. The distal limb of the loop then passed

to the cerebellum below or between the nerves. In several specimens complicated loopings at the entrance to the meatus increased the complexity and intimacy of the neurovascular relations at that site.

In 13 per cent. of the specimens the artery did not extend as far laterally as the meatus but passed above (1 per cent.), between (5 per cent.), or below (7 per cent.) the facial and auditory nerves to reach the cerebellum. In approximately 23 per cent. of the specimens the artery was absent or was not related significantly to the nerves. When the anterior inferior cerebellar artery passed between the nerves it usually did so between the motor division and portio intermedia of the facial nerve.

The intimate relationship of a large arterial channel to the facial and auditory nerves in such a confined space as the internal auditory orifice and canal are anatomical features of considerable practical importance in connexion with surgical exploration of the cerebello-pontine angle and certain disturbances of nerve function which may possibly arise as a direct consequence of mechanical pressure exerted on the nerves by atheromatous, enlarging, abnormally pulsating, or tortuous vessels.

Watt and McKillop (1935) have also directed attention to the passage of the artery over, under, and between the nerves in the cerebello-pontine angle. They concluded that, in effecting this relationship, "the anterior inferior cerebellar artery usually lies close to the surface of the brain" but that "the passage is sometimes made far from the brain surface, close to the mouth of the internal auditory meatus." It is believed that they missed the significance of the relation to the meatus because their observations were made on brains already removed from the cranium. Stibbe (1939) described and illustrated the varying relations of the anterior inferior cerebellar artery to the seventh and eighth nerves in the cerebello-pontine angle but stressed that the most proximal part of the nerve is relatively free from arteries.

Internal Auditory Artery.—The internal auditory artery arose from the basilar artery in 17 per cent. of the specimens (Stopford, 36 and 28 per cent. on the right and left sides respectively; Watt and McKillop, 5 per cent.). In these cases the vessel crossed the cerebello-pontine angle in front of or above the nerves, although usually situated some distance from them. The artery maintained this relative position as it passed along the meatus where the neurovascular relationship was a more intimate one than in the cerebello-pontine angle.

In the remaining 83 per cent. of the specimens the vessel took origin from either the apex or the proximal limb of the first arterial loop formed by the anterior inferior cerebellar artery. The intimacy of the neurovascular relationship was consequently determined by the disposition of the anterior inferior cerebellar artery in the cerebello-pontine angle or in the meatus and by the site of origin of the internal auditory artery from that channel. In general the branch coursed in front of or above the nerves and was more intimately related to them in the meatus than in the cerebello-pontine angle.

Posterior-Inferior Cerebellar Artery.—The posterior-inferior cerebellar artery frequently loops upwards ventral to the facial and auditory nerves at their site of origin, where it may compress them backwards against the pons or the middle cerebellar peduncle (Fig. 9).

TABLE II

RELATIONSHIP OF THE ANTERIOR-INFERIOR CEREBELLAR ARTERIES TO THE ABDUCENT NERVES

Relationship	No.
1. *Artery related to the nerve on both sides :*	
Both anterior*	123
Both posterior	6
Right anterior, left posterior	30
Right posterior, left anterior	10
2. *Artery related to the nerve on one side only :*	
Left : anterior	6
posterior	1
Right : anterior	9
posterior	1
3. *Duplication of the artery :*	
(*a*) Bilateral	
Both arteries anterior on the right and left	1
Right : both arteries posterior Left : both arteries anterior	1
Right and Left : one anterior and one posterior to the nerve	1
Right : both arteries anterior Left : one anterior and one posterior	1
(*b*) Unilateral	
(i) Two arteries on the right and one on the left.	
Right : both anterior Left : anterior	2
Right : anterior and posterior Left : anterior	1
Right : anterior and posterior Left : posterior	1
(ii) Two arteries on the left and one on the right.	
Right : anterior Left : both anterior	3
Right : anterior Left : anterior and posterior	4
4. *Artery absent on both sides or not related to the nerves*	9
Total	210

* In three of these specimens the artery pierced the nerve on the left side.

Basilar and Vertebral Arteries.—Deviation of the basilar artery from the mid-line occasionally takes this vessel not only anterior to the abducent nerve but into contact with the facial and auditory nerves. Dandy (1944) has also observed that "the lateral bend in the basilar artery may come to rest either upon the trigeminal or auditory nerve."

A tortuous vertebral artery may deform the ponto-medullary junction at the site of origin of these nerves and in this way compress them (Figs. 13 and 14). Such a condition was observed in this series on 7 occasions on the right side and 20 on the left.

The Glossopharyngeal, Vagus, Accessory, and Hypoglossal Nerves

The glossopharyngeal, vagus, accessory, and hypoglossal nerves are related to the vertebral and posterior inferior cerebellar arteries in the interval between the medulla medially and the jugular and hypoglossal foramina laterally.

Vertebral Arteries.—Thickened atheromatous vertebral arteries were observed arching forcibly backwards into the interval outlined between the olive medially and the flocculus laterally. The vessel thereby forced the glossopharyngeal, vagus, accessory, and hypoglossal nerve rootlets acutely backwards and compressed them against the medulla as they passed round the artery on their way to their respective foramina. The deformation thereby produced was considerable (Fig. 13). This condition was present in this series on the right side in seven specimens and on the left side in twenty.

Table III

Relationship of the Vertebral and Basilar Arteries to the Abducent Nerves

Relationship	No.
1. *Basilar Artery :*	
Anterior to the right nerve	3
Anterior to the left nerve	6
Anterior to both nerves	1
2. *Vertebral Artery :*	
Right vertebral artery	
Anterior to the right nerve	11
Anterior to the left nerve	1
Left vertebral artery	
Anterior to the left nerve	21
Both vertebral arteries	
Anterior to the right nerve	1
3. *Basilar and Vertebral Arteries :*	
Anterior to the left nerve	
Basilar and both vertebral arteries ..	1
Basilar and right vertebral arteries ..	1
Total ..	46

Posterior-Inferior Cerebellar Arteries.—Each posterior-inferior cerebellar artery follows a variable and very tortuous course, with complicated loopings, as it runs dorsally between the emerging glossopharyngeal, vagus, accessory, and hypoglossal nerve rootlets to reach the interval between the restiform body and the cerebellum. Though the artery is variably related to the emerging rootlets as it courses dorsally, the relationship is always an intimate one and is frequently of such a character as to lead to the deformation and stretching of the nerve rootlets.

References

Batujeff, N. (1889). *Anat. Anz.*, **4,** 282.
Beadles, C. F. (1907). *Brain*, **30,** 285.
Blackburn, I. W. (1907). *J. Comp. Neurol.*, **17,** 493.
Collier, J. (1904). *Brain*, **27,** 490.
Cushing, H. (1911). *Ibid*, **33,** 204.
Dandy, W. E. (1939). *J. internat. Coll. Surg.*, **2,** 5.
——(1944). "Intra-cranial Arterial Aneurysms." Comstock Publishing Co., New York.
Decker, F. (1886). Quoted by Oertel.
De Vriese, B. (1904). *Anat. Anz.*, **25,** Suppt. 88.
Duret, H. (1874). *Arch. Physiol. norm. Pathol.*, **6,** 60, second series. Quoted by Oertel.
Fawcett, E., and Blachford, J. V. (1906). *J. Anat. Physiol.*, **40,** 63.
Fearnsides, E. G. (1916). *Brain*, **39,** 224.
Flesch, M. (1882). Quoted by Oertel.
Fuchs, E. (1924). "Textbook of Ophthalmology." Eighth Edit. J. B. Lippincott Co., Philadelphia. p. 100.
Hochstetter, F. (1885). Quoted by Oertel.
Jefferson, G. (1937). *Brain*, **60,** 444.
Oertel (1922). *Anat. Anz.*, Supplement to Vol. 55, p. 281.
Peacock, T. B. (1876). *St. Thomas's Hosp. Rep.*, **7,** 119 and 317.
Quain, R. (1844). "The Anatomy of the Arteries of the Human Body." London. p. 507.
Smith, G. Elliot (1905). *Rev. Neurol. Psychiat.*, **3,** 182.
——(1909). *J. Anat. Physiol.*, **43,** 310.
Stibbe, E. P. (1939). *Lancet*, **1,** 859.
Stopford, J. S. B. (1915). *J. Anat. Physiol.*, **50,** 131.
Sunderland, S. (1941). *Aust. N.Z. J. Surg.*, **11,** 140.
——(1945). *Brain*, **68,** 23.
Symonds, C. P. (1923). *Guy's Hosp. Reps.*, **73,** 139.
Tareniecki (1880). Quoted by Oertel.
Traquair, H. M. (1938). "An Introduction to Clinical Perimetry." Henry Kimpton, London.
Tüngel (1860). Quoted by Oertel.
Valenti. Quoted in Poirier P. and Charpy, A.: "Traité d'Anatomie Humaine." Masson et Cie, Paris.
Watt, J. C., and McKillop, A. N. (1935). *Arch. Surg.* **30,** 336.
Windle, B. C. A. (1888). *J. Anat. Physiol.*, **22,** 289.
Wolff, E. (1928). *Brit. J. Ophthalmol.*, **12,** 22.

DIABETES INSIPIDUS FOLLOWING CLOSED HEAD INJURY

BY

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Diabetes insipidus is a rare disease and it is a very uncommon sequel of head injury. Fitz (1914) found that the incidence of the disease attributable to any cause was fourteen cases per hundred thousand admissions to a general hospital, and Rowntree (1924) found thirteen cases per hundred thousand admissions to the Mayo Clinic. Rabinowitch (1921) found one case of diabetes insipidus among fifty thousand admissions to a general hospital. In only two of fifty-six cases reported by Rowntree (1924) and two, or possibly three, of forty-two cases reported by Jones (1944) was the diabetes insipidus due to head injury. Rand and Patterson (1937) have stressed the rarity of post-traumatic diabetes insipidus by stating that no case occurred in one hundred and fifty thousand admissions to a neurosurgical unit.

Kahler (1886) reported twenty-six cases of diabetes insipidus following head injury, and Rand and Patterson (1937) recorded six cases; the majority of reports on the clinical features of the condition, however, have been based on one or two cases. Fink (1928), Turner (1928), and Warkany and Mitchell (1939) have reviewed the literature, and Riddoch (1938), Symonds (1943), and Rowbotham (1945) have recorded their impressions. It is the most common hypothalamic disorder following trauma. The injury has usually been severe and the skull fractured, the fracture generally involving the base. Thirst and polyuria begin a few days to several months after the injury. The severity of the symptoms varies from case to case, and may fluctuate in some patients. Fever sometimes improves the condition. The duration of the symptoms cannot be predicted, but most cases do recover. The response to pituitrin therapy is usually good, but sometimes symptoms are only partly relieved and in a few cases it has no effect. Other evidence of hypothalamic injury is sometimes present, a reduction in perspiration and obesity, and disturbance in sex functions. Cranial nerves are often involved, the optic and oculo-motor being those most commonly affected.

Of all non-fatal closed head injuries (gunshot wounds and those with dural penetrations excluded,) admitted to the Military Hospital for Head Injuries, Oxford, during the years 1940–45, which numbered about five thousand, thirteen suffered from diabetes insipidus. We have had the opportunity of studying three (Cases 5, 9, and 12) of these personally, the records of the other ten, and the records of five cases (Cases 14–18) treated in the Nuffield Department of Surgery, Oxford, under Professor Sir Hugh Cairns. This series of eighteen cases is reviewed in an attempt to add to our present rather inadequate knowledge of the clinical features and pathology of the condition.

The Table indicates the relevant features in each case.

Site of Trauma and Severity of Injury

The site of injury was judged by the position of cutaneous abrasions, bruises, or lacerations of the scalp or face, taking into consideration the position of fractures when present, and in all but three cases it was possible to determine with reasonable certainty the site at which the head was struck. In nine cases the blow was frontal, in six occipital. In twelve cases the skull was fractured—six in the frontal area, four in the occipital, and two in the middle fossa.

The severity of a closed head injury is difficult to assess and depends on several factors. The best single guide to severity, however, is the duration of the post-traumatic amnesia (P.T.A.) to which the degree of residual disability often bears a direct relationship, and Russell (1942) classifies cases with P.T.A. less than two hours as slight, two to forty-eight hours as moderate, and over two days as severe. It is seen that the majority of our cases

TABLE

DETAILS OF CASES

Case No.	Age	Nature of injury and date	Site of injury	P.T.A. in days	Diabetes insipidus				Associated hypothalamic or pituitary disorder	Associated injury to			Radiograph of skull
					Day of onset after injury	Duration (months)	Maximum recorded 24-hour output of urine (oz.)	Response to pituitrin		Olfactory nerves	Optic nerve	Optic chiasm	
1	27	Motor cycle accident 16.3.40	Occipital	19	9	1	150+	Yes	—	+	—	—	Nothing abnormal
2	21	Motor car accident 6.11.42	Frontal	24	16	5/30	150+	Yes	—	—	—	—	Nothing abnormal
3	20	Lorry accident 20.10.42	Occipital	7	31	1	180	Yes	—	+	+	—	Nothing abnormal
4	19	Road accident 20.10.41	Occipital	17	12	1	200+	Unknown	Pathological laughter	—	—	—	Vertical fissured fracture occipital
5	27	Motor car accident 15.6.45	Frontal	21	18	4	362	Yes	—	+	—	+	Fracture roof of right orbit running into frontal sinus; fracture nasal bones
6	19	Fall 30 ft. 25.2.41	Frontal	21	15	5	280	Yes	—	+	—	+	Fissured fracture frontal involving sinus
7	20	Aeroplane crash 10.4.43	Unknown	5 *T*	10	2	?	Yes	—	—	—	—	Nothing abnormal
8	26	Lorry accident 28.7.42	Frontal	2/24	14	6½	250	Yes	—	+	—	—	Fractured right frontal involving sinus
9	39	Bomb blast: thrown forward 8.4.41	Frontal	13	13	9	?	Unknown	Adiposo-genital syndrome	+	—	—	Nothing abnormal
10	38	Fell backward striking head on stone floor	Occipital	10	10	7	150+	Yes	—	+	—	—	Fissured fracture left occipital
11	37	Road accident 28.10.44	Occipital	>21	17	>22	200	Yes	Outbursts of rage	—	—	—	Fissured fracture left occipito-parietal
12	34	Car accident 12.10.45	Frontal	7	30	>13	350	Yes	Anterior pituitary deficiency	—	—	+	Nothing abnormal
13	36	Car accident 19.11.40	Frontal	2	11	>38	465	Yes	—	+	—	—	Fissured fracture left frontal; both maxillæ and right zygoma
14	27	Road accident 6.7.44	Occipital	3	?	>15	?	Unknown	—	+	—	—	Vertical fissured fracture occipital into foramen magnum
15	20	Bomb blast 15.7.44	Frontal	5	7 to 14	>12	500	Yes	—	—	—	—	Fissured fracture frontal
16	22	Fall from bus 2.5.44	Unknown	10	14 to 28	>30	600	Yes	—	—	—	—	Fissured fracture temporal running into middle fossa
17	30	Car accident 1935	Frontal	21	?	>96	400	Yes	—	+	—	+	Fissured frontal fracture maxilla and mandible
18	19	Car accident 22.9.38	Unknown	21	?	2	320	Unknown	—	+	—	+	Bridged bella ? interruption in continuity of petro-clinoid ligaments

suffered very severe injuries. In five only was the P.T.A. less than one week, and in only one of these was it less than two days.

Onset, Course, and Treatment of Diabetes Insipidus

Accuracy in determining the time of onset of diabetes insipidus is difficult, since so often the patients are confused and incontinent in the early stages after the injury. Moreover, limitation of fluid intake, which occurs if the patient is unable to demand extra drink, masks the condition. The symptoms were first noticed by the staff, or complained of by the patients, from nine to thirty-one days after the injury. In six cases the diagnosis was made with the aid of fluid intake and output charts before the period of post-traumatic amnesia was judged to have ended, and in two cases it was diagnosed on the day it ended. It might be argued that in these cases it had been present since the injury, but unnoticed. In the remaining five cases it was possible to estimate the time of onset more accurately, because there was a clear interval of from five to twenty-two days during which the patients were fully orientated and rational, before they complained of symptoms. There was, therefore, in these cases, a definite delay in the onset of the disease.

The degree of polyuria and polydipsia may at first be mild, and may reach the maximum days or even weeks later. Precise information is not available in most of our cases regarding fluctuations in the severity of the condition, because the natural course of the disease was usually altered by therapy. In three cases, however, we have information concerning the development of the disease. The symptoms were first noticed in one (Case 5) eighteen days after the injury, when the urinary output was 160 oz.; it gradually increased, and reached the maximum recorded output of 362 oz. four days later, when treatment with pituitrin was started. In Case 12 the measured urinary output showed a steady increase to a maximum of 400 oz. eight days after the onset of symptoms. The third (Case 8) was noticed to have excessive thirst and increased urinary output, 160 oz. fourteen days after the injury, but it was not till five and a half weeks later that he complained of symptoms, by which time the output of urine had shown a steady increase to 250 oz. and treatment was started.

The course of the disease varied in severity and duration. The majority, eleven, recovered spontaneously within nine months of the onset. Of the remaining seven cases, one (Case 14) was improving and had only mild symptoms fifteen months after the onset, and the other six showed no sign of recovery. Three of the unchanged cases (Cases 11, 12, and 15) were observed for thirteen to twenty-two months. In the other three cases (Cases 13, 16, and 17) with persistent diabetes, the disease was considered to be permanent as it had been present for longer than two and a half, three, and eight years respectively.

Fourteen cases were treated with posterior pituitary extract, either hypodermically or as snuff, and complete relief of symptoms resulted in all of them, provided adequate dosage was used. The response to pituitary therapy is not known in four cases, either because recovery had occurred (Cases 9 and 18) before the patients came under observation, or because treatment was considered unnecessary as improvement was already taking place and symptoms were not troublesome (Cases 4 and 14). No cases resistant to pituitrin were encountered.

Associated Intracranial Damage

Injuries to the olfactory nerves and optic chiasm or nerves were striking in their frequency. More than half (eleven cases) suffered from bilateral anosmia, five had visual field defects characteristic of a chiasmal lesion, and one had damage to the right optic nerve. No other signs of focal intracranial damage were common, and evidence of hypothalamic disorder, other than diabetes insipidus, was uncommon. One patient only (Case 9) presented other undoubted evidence of hypothalamic dysfunction, an adiposo-genital syndrome, which gradually developed during the first fifteen months following the injury. Two cases (Cases 4 and 11) showed emotional abnormality of a type which suggested a hypothalamic lesion, and in one case (Case 12) there was evidence of anterior pituitary dysfunction.

The infrequency of other hypothalamic syndromes following head injury is remarkable. When the material for this study was being collected, the records of all surviving cases of closed head injury at the Hospital for Head Injuries that had been indexed as having evidence of hypothalamic damage were examined, and all thirteen were found to have diabetes insipidus. Minor or transitory manifestations of hypothalamic disorder may have been missed, but it is highly improbable that such conditions as narcolepsy, impotence, or adiposo-genital syndrome would have been overlooked, even if they occurred as late symptoms, since the majority of cases have been followed up for more than two years and many for four years.

Comment

Riddoch (1938) and Symonds (1943) have stated that diabetes insipidus is the most common disorder

of hypothalamic function following closed head injury, and the evidence in this series strongly supports this view. It usually follows severe trauma to the front or back of the head, the same type of injury which has previously been shown to result most commonly in damage to the olfactory nerves, optic chiasm and nerves (Russell, 1943 ; Leigh, 1943 ; Traquair and others, 1935 ; Turner, 1943).

There appears to be no relationship between the severity of the injury and the delay in onset of the diabetes insipidus or its duration.

Although the precise mode of action of the posterior pituitary anti-diuretic hormone is not understood, there is general agreement that the gland is stimulated to secrete by nerve impulses passing to it from the supra-optic and paraventricular nuclei in the anterior hypothalamus via the supra-optic hypophyseal tract in the pituitary stalk. Experimentally, it has been shown that a bilateral lesion of these neurones is necessary for the production of diabetes insipidus (Fisher and others, 1938 ; Heinbecker and White, 1941 ; Magoun and Ranson, 1939). In these cases the polyuria is controlled by pituitrin, and Dandy (1940) has shown that section of the pituitary stalk in man can result in permanent diabetes insipidus which responds to pitruitin. There are rare cases of diabetes insipidus unresponsive to pituitrin which Dreyfus (1931) suggested occurred only when the tubero-mamillary nuclei are damaged.

In experimentally produced diabetes insipidus there is a delay in onset of the permanent polyuria, usually six to twenty-two days (Biggart and Alexander, 1939 ; Fisher and others, 1938 ; Heinbecker and White, 1941), but it may be as long as six or ten weeks (Fisher and others, 1938). Heinbecker and White (1941) have shown in dogs that this delay can be abolished by removing all the pitressin-secreting tissue at operation, this suggesting that the latent period represents the time during which the denervated neuro-hypophysis produces pitressin. They also showed that the severity of the polyuria depended on the extent of damage to the supra-optic hypophyseal connexions, maximum and permanent polyuria following complete section ; but, provided 15 per cent. of the fibres remained intact, the dogs recovered from their diabetes insipidus.

Holbourn (1943), in his studies on the mechanism of head injury, stresses the importance of changes in rotational velocity of the head, drawing the analogy of a full flask of water suddenly rotated, when it can easily be seen that the water tends to stay behind and only the flask rotates. Russell (1932) has suggested that movement of the brain relative to the skull at the time of injury may account for the frequency of anosmia in occipital injuries from tearing of olfactory filaments as they pass through the cribiform plate of the ethmoid. Traquair and others (1935) consider that the same mechanism may account for chiasmal lesions through the tearing of the small pial blood vessels supplying the chiasma. They also suggest that hypothalamic lesions may be produced in this way. It would seem likely, however, that in such an antero-posterior displacement or rotation of the brain within the skull the supra-optic hypophyseal connexions lying superficially in the anterior hypothalamus and in the pituitary stalk might be injured by being stretched, since the pituitary is held rigidly in the sella turcica.

There is no doubt that in the present series of cases the onset of diabetes insipidus was delayed, and this might suggest that the neurones are not damaged at the time of injury but are interfered with by a delayed pathological process, for example, organizing blood clot round the pituitary stalk on pressure from an arachnoid cyst (Kourilsky and others, 1942). However, the delay in onset is consistent with experimental observation and does not rule out neuronal damage at the time of injury. It is interesting to notice in this connexion that the period of delay in our cases corresponds fairly closely to that found in experimental animals.

The pathology probably varies in different cases. Laceration of the hypothalamus or pituitary by a displaced fragment of bone, or tearing by separation of a fracture of the sphenoid, are very improbable in our cases, for in none was there radiological evidence of a fracture involving the sphenoid or of a displaced bone fragment at the base of the brain. Interference with the blood supply to the hypothalamus from tearing of the fine pial vessels might account for some cases, but if this were a usual mechanism it would be strange that other hypothalamic syndromes are not encountered more frequently. An arachnoid cyst in the chiasmal region has been found at operation to be the cause of diabetes insipidus (Kourilsky and others, 1942), and the symptoms have been relieved immediately by incision of the cyst. However, one would expect pressure from a cyst or constriction of the pituitary stalk from organized blood clot to result in a permanent diabetes insipidus unless the pressure were relieved surgically, and it is seen that the majority of cases undergo spontaneous recovery within nine months. We think it probable, therefore, that the lesion is most commonly in the pituitary stalk, due to stretching from displacement of the brain at the time of injury, and that the duration of symptoms and severity of the diabetes

insipidus may depend on the extent of neuronal damage in the supra-optic-hypophyseal tract. The rarity of other hypothalamic syndromes and of permanent refractory diabetes insipidus is probably due to the high mortality rate from more extensive injury to this part of the brain.

Summary

1. Eighteen cases of diabetes insipidus following closed head injury have been studied and the relevant features tabulated.

2. In fifteen in which the site of injury could be determined it was frontal or occipital.

3. The symptoms were usually first noticed during the second or third week after injury.

4. All cases treated responded to pituitrin.

5. Spontaneous recovery took place in the majority, in eleven within nine months.

6. Associated injury to the olfactory nerves and optic chiasm is common; other hypothalamic syndromes are rare.

7. The mechanism of the injury is discussed, and it is suggested that a traction lesion of the pituitary stalk would best explain most cases.

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References

Beattie, J. (1938). In Clark, W. E. Le Gros, and others: "The Hypothalamus." Oliver. Boro, Edinburgh. p. 69.

Biggart, J. H., and Alexander, G. L. (1939). *J. Path. Bact.*, **48**, 405.

Dandy, W. E. (1940). *J. Amer. med. Ass.*, **114**, 312.

Dreyfus, G. G. (1931). "Le Diabete Insipide." Doin, Paris. Quoted by Beattie.

Fink, E. B. (1928). *Arch. Path.*, **6**, 102.

Fisher, C., Ingram, W. R., and Ranson, S. W. (1938) "Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance." Edwards Brothers, Inc., Ann Arbor, Michigan.

Fitz, R. (1914). *Arch. intern. Med.*, **14**, 706.

Heinbecker, P., and White, H. L. (1941). *Amer. J. Physiol.*, **133**, 582.

Holbourn, A. H. S. (1943). *Lancet*, **2**, 438.

Jones, G. M. (1944) *Arch. intern. Med.*, **74**, 81.

Kahler, O. (1886). *Z. Heilk.*, **7**, 105. Quoted by Fink.

Kourilsky, R., David, M., Sicard, J., and Galey, J. J. (1942). *Rev. Neurol.*, **74**, 264.

Leigh, A. D. (1943). *Lancet*, **1**, 38.

Magoun, H. W., and Ranson, S. W. (1939). *Trans. Amer. Neurol. Ass.*, **65**, 63.

Rabinowitch, I. M. (1921). *Arch. intern. Med.*, **28**, 355.

Rand, C. W., and Patterson, G. H. (1937). *Bull. Los Angeles Neurol. Soc.*, **2**, 163.

Riddoch, G. (1938). In Clark, W. E. Le Gros and others: "The Hypothalamus." Oliver. Boro, Edinburgh. p. 119.

Rowntree, L. G. (1924). *J. Amer. med. Ass.*, **83**, 399. Quoted by Rand and Patterson.

Rowbotham, S. F. (1945). "Acute Injuries of the Head." Second Edit. p. 300.

Russell, W. R. (1932). *Brain*, **55**, 549.

——(1943). In Brock's "Injuries of the Skull, Brain, and Spinal Cord." London. p. 104.

——(1942). *Brit. med. J.*, **2**, 521.

Symonds, C. P. (1943). In Brock's "Injuries of the Skull, Brain, and Spinal Cord." London. p. 65.

Traquair, H. M., Dott, N. M., and Russell, W. R. (1935). *Brain*, **58**, 398.

Turner, J. H. (1928). *Arch. Pediat.*, **45**, 433.

Turner, J. W. A. (1943). *Brain*, **66**, 140.

Warkany, J., and Mitchell, A. G. (1939). *Amer. J. Dis. Child.*, **57**, 603.

CEREBRAL THROMBOPHLEBITIS AND FIBRINOGEN B

BY

GILBERT PHILLIPS

(RECEIVED MAY 14, 1948)

Thrombophlebitis of the superficial cerebral veins and the dural venous sinuses is now a well-recognized complication of infective processes, not only about the head and neck but elsewhere in the body (Symonds, 1931, 1937, 1940; Purdon Martin and Sheehan, 1941; Purdon Martin, 1941). Most observers, however, have realized the difficulty in establishing the final pathological diagnosis, particularly in the early stages where the patient may present with high bilateral papillœdema and no abnormal physical signs, or with some evidence of increased intracranial pressure and paretic or convulsive phenomena. It is always important in those cases in which visual acuity is deteriorating rapidly as the result of papillœdema to exclude a space-occupying lesion within the skull, as it is not otherwise safe to embark upon a course of repeated spinal drainage in order to save a patient's vision. The diagnostic difficulties are well illustrated in the following case:

Case A

A boy, aged 6 years, had nothing relevant in the past history. He had suffered from attacks of morning vomiting and anorexia for two months. These had been episodic, the one for which he was admitted to hospital having lasted for four days. The provisional diagnosis was anorexia nervosa or intracranial lesion. On admission, the child was very quiet, thin and wasted. He talked slowly, but there was no dysarthria. There was no history of middle-ear infection or tonsillitis. Full clinical examination did not reveal any significant abnormality, apart from high bilateral papillœdema (3 diopters). The ophthalmologist considered that the papillœdema was of recent origin. A radiograph of the skull showed no abnormality. The urine was clear and the Mantoux reaction negative. The blood sedimentation rate was 90 mm. in the first hour, 120 mm. in the second. The cerebrospinal fluid was under greatly increased pressure (400 mm.). The fluid was clear; there were six lymphocytes per c.mm.; the total protein was 70 mg. per 100 c.cm., and the chloride 750 mg. per 100 c.cm.; there was no increase in globulin. The fluid was incubated and proved sterile. A blood count showed $4{\cdot}2 \times 10^6$ red blood cells, hæmoglobin 12·5 g., leucocytes 8,500 per c.mm. of blood (neutrophils 55 per cent., lymphocytes 33 per cent., mononuclears 10 per cent., and eosinophils 2 per cent.). In view of the high papillœdema and the episodic vomiting, it was considered that the child might have a tumour in the vermis of the cerebellum, and at that stage the author was asked to see the case in consultation. Previous clinical findings were checked, and it was confirmed that there were no signs of cerebellar dysfunction. The teeth were grossly decayed, with large carious pockets and extensive gingivitis. In view of previous experience with a similar case recorded some time ago (Phillips, 1935), it was suspected that the hydrocephalus might be secondary to cerebral thrombophlebitis due to the oral sepsis, and full dental hygiene was carried out. The carious teeth were extracted and the gingivitis cleared up. Within the following week the papillœdema began to subside, and when the child was examined fourteen days later the discs had returned almost to their normal appearance.

In this case, although the diagnosis is based on presumptive evidence, there is little doubt that the oral sepsis was the primary cause of the intracranial lesion which led to the production of increased intracranial pressure.

In view of the work by Cummine and Lyons (1947) in the estimation of fibrinogen B in cases of intravascular thrombosis, it was decided to carry out an estimation of fibrinogen B in the blood in a series of cases of suspected cerebral thrombophlebitis. The purpose of this article is to present the case histories of this series and the conclusions which were drawn from the results of this examination. The following cases have come under the author's care during the past three months.

The Author's Cases

Case 1.—A woman, aged 22 years, complained of blurred vision for one month. The onset was sudden. She awoke one morning feeling sick and wanted to vomit. Her neck was stiff and vision very blurred. She began to suffer from severe frontal headaches each morning, and the vision became progressively worse. There was nothing significant in her previous history, apart from the fact that since the birth of her last child fifteen months before she had put on 4 stone in weight. There had been no fits. There was no polyuria or polydypsia. Her periods were regular. She had a purulent vaginal discharge. There was nothing relevant in the family history. The patient was an obese young woman, intelligent and co-operative. She could only detect moving objects and was unable to count the number of fingers held before her eyes. Eye movements were full. There was no nystagmus. She had marked bilateral papillœdema (2 diopters). The pupils were equal, central, and circular, and reacted to light. Full neurological examination revealed no abnormality,

apart from diminished abdominal reflexes on the left side. The cardiovascular system was normal. A blood count showed 7,650 white cells per c.mm. of blood (54 per cent. neutrophils and 34 per cent. lymphocytes).

The preliminary impression recorded states: "A review of the history suggests Quincke's syndrome, but there is no history of infection in the teeth, sinuses, or tonsils, although the latter have not been removed." Radiograph of the skull did not reveal any evidence of an intracranial lesion. In view of the papillœdema and the transient polyuria, a ventriculogram was performed and the ventricles were found to be small, at the normal depth, and the fluid under greatly increased pressure. A considerable quantity of cerebrospinal fluid escaped from beneath the arachnoid, confirming the presence of an external hydrocephalus. Air studies showed a normal ventricular system. A diagnosis of cerebral thrombophlebitis was then recorded. Lumbar puncture showed a pressure of 420 mm., and repeated spinal drainage was performed, the pressure being reduced half way towards normal on each occasion. The following initial pressures were recorded successively: 500 mm., 270 mm., 190 mm., 230 mm., 190 mm., 165 mm., and 120 mm. Following these spinal drainages, the patient's vision progressively improved and the papillœdema subsided. On discharge from hospital the patient felt perfectly well and her vision had returned to normal.

In this case, no evidence of a focal sepsis could be detected, apart from the fact that the patient had a profuse purulent vaginal discharge, which had been present since the birth of her child twelve months previously.

Case 2.—A woman, aged 25 years, had been quite well until some weeks previously, when she noticed that she had difficulty in lifting the right leg when walking, and the leg became progressively weak. She had shown increasing drowsiness, and complained of a feeling of numbness in the right arm. In the last week she had noticed some blurring of vision, generalized dull headaches, and giddiness. There was nothing relevant in her previous history. No abnormal signs, apart from bilateral papillœdema and a small hæmorrhage in the right disc, were found on examination. She gave a history of repeated sore throats, and radiographs of the nasal sinuses showed dullness in the right antrum. The lung fields were clear radiographically. Lumbar puncture showed clear fluid under a pressure of 220 mm., with four lymphocytes per c.mm.; the total protein was less than 20 mg. per 100 c.cm.. The white cell count was 8,050 per c.mm. with 61 per cent. neutrophils and 35 per cent. lymphocytes. No abnormality was seen in the radiographs of the skull. Ventriculography was decided upon to exclude a space-occupying intracranial lesion. There was a considerable quantity of subarachnoid fluid, which escaped when the dura was opened, but the ventricles appeared to be normal in size and depth. Air studies showed a normal ventricular system. A diagnosis of cerebral thrombophlebitis was made, and the patient was treated by repeated lumbar punctures, and was given 10,000 units of heparin by injection. Intracranial pressure gradually subsided to 150 mm., the discs returned almost to normal in the succeeding fortnight, and the vision improved. The patient still complained of some weakness in the right leg on walking any distance.

Case 3.—A man, aged 37 years, was well until four weeks before admission to hospital, when he began to suffer from generalized headaches, which became severe and settled down in the frontal area. Just before admission he had an attack in which his right arm and hand gave a few coarse twitches, and the next thing that he remembers was that he became conscious in hospital. His wife had witnessed the initial fit, and stated that convulsive movements began in the right hand and proceeded up the arm and down the right side to the right leg. He then had a generalized seizure, in which he passed urine and remained unconscious for about half an hour. Two weeks after admission he had a similar fit, and he had three Jacksonian seizures in the right hand in the next fortnight. During this time he complained of blurred vision, which became progressively worse. He said he had had left-sided pleurisy and pneumonia annually for five years previously. He had venous thrombosis in both legs on a number of occasions, and an infected varicose ulcer on the right leg during the past six months. Examination showed well-marked papillœdema of three diopters in both discs, with considerable increase in the blind spots but no contour defect in the visual field. There were no other abnormal neurological signs. There were 11,050 white cells per c.mm. of blood, with 73 per cent. neutrophils, 19 per cent. lymphocytes, and 8 per cent. monocytes. Radiographically the lung fields were clear. There was no evidence of dental sepsis, and no lesion could be detected in the skull. Lumbar puncture revealed a clear fluid under a pressure of 600 mm., with 10 lymphocytes per c.mm., and a protein of 20 mg. per 100 c.cm. A ventriculogram revealed copious fluid in the subarachnoid space, and the ventricles were normal in size, shape, and position. The second lumbar puncture five days later revealed a pressure of 380 mm., which was reduced by drainage to 160 mm. Repeated lumbar puncture did not produce much reduction of the intracranial pressure, and Mr. Lister Reid performed a left subtemporal decompression, when the brain was found to be under considerably increased tension and bulged out into the decompression opening. The ventricles were again tapped at this operation, and a small quantity of cerebrospinal fluid escaped under considerably increased pressure. At this stage the author was asked to see the case in consultation, and formed the opinion that the patient was suffering from cerebral thrombophlebitis.

Case 4.—A boy, aged 7 years, was well until December, 1947, when he began to suffer from stiffness in the neck. During the succeeding fortnight he also complained of abdominal pain, and on Jan. 27, 1948, he developed an internal strabismus of the left eye. Examination of the fundi showed a high bilateral papillœdema. His temperature was 99·4° F. Lumbar puncture disclosed greatly increased pressure of over 400 mm.; the cerebro-

spinal fluid was clear and contained one leucocyte per c.mm. ; chlorides were 720 mg. per 100 c.cm. and the globulin test negative. The fluid was sterile on culture. A radiograph of the sella turcica did not disclose any abnormality. The boy's general condition remained good until Feb. 5, when his vision began to deteriorate. He was flown to Sydney, and, on admission to hospital here on Feb. 9 he was found to have gross papillœdema with hæmorrhages in each disc. His visual acuity in the right eye was 6/36 and in the left 6/24. There was bilateral sixth nerve palsy, and he had some ataxia in the left hand. Apart from this, there was no abnormal neurological abnormality. There was no evidence of lead intoxication. Radiographs of the long bones were clear. There was no punctate basophilia. The lumbar puncture pressure under Avertin was over 600 mm. A provisional diagnosis of cerebral thrombophlebitis was made, but, in order to exclude a vermis tumour, ventricular estimation was performed. Copious subarachnoid fluid was found, determining a state of external hydrocephalus, and the lateral ventricles, when needled, were found to be small and to contain clear fluid under high pressure.

From Feb. 20 to March 5, this boy had daily lumbar punctures at first, then three times weekly. On each occasion large quantities of clear cerebrospinal fluid were removed, averaging about 20 to 30 c.cm. The pressure and papillœdema gradually subsided, and his visual acuity rapidly returned to normal.

Case 5.—A woman, aged 39 years, had complained of frontal headaches for some years, but during the past few months had noticed progressive deterioration of vision and had consulted an ophthalmologist, who detected bilateral papillœdema. Full neurological investigation did not reveal any abnormality, apart from bilateral papillœdema of three diopters. The blood pressure was 160/90 mm. Hg. A full blood count was within normal limits. Blood urea was 32 mg. per cent. Lumbar puncture pressure was 380 mm., with a protein content of 20 mg. per 100 c.cm., no cells, and a negative Wassermann reaction. A radiograph of the skull did not reveal any significant abnormality apart from marked hyperostosis diffusa. In appearance the patient was a very short, rather stout female, with fine hair and pale, waxy skin. In order positively to exclude a space-occupying lesion, ventriculography was carried out, and this disclosed an external hydrocephalus with a small ventricular system, which was normal in size, shape, and position. In view of this finding, the diagnosis of cerebral thrombophlebitis was made, although there was no obvious infective focus present. The teeth, tonsils, and sinuses were excluded, and the urinary tract was free from infection. A Graham's test, however, showed no concentration of the drug in the gall bladder, with a faint outline of a large gallstone in the neck. She was given an intravenous injection of 5 c.cm. of heparin, which was repeated on two occasions, and at the same time a course of Dicoumarol was begun. Repeated lumbar punctures showed a gradually falling intracranial pressure, which subsided to normal six weeks after admission, at which time she was discharged with normal fundi and free from her headaches. Cholecystectomy has been advised.

Case 6.—A baby boy, aged 15 months, was well until three weeks before admission to hospital on April 22, 1948, when he had a red injected throat accompanied by fever. The child was drowsy and developed a cough, and vomiting occurred several times each day. He lost weight and became dehydrated. On March 11, 1948, he developed left facial paresis, and there was some suspicion of weakness in the extremities of the left side. A course of penicillin, 5 per cent. glucose in saline, was given by intravenous drip. Repeated blood counts did not reveal any significant abnormality, and there was no leucocytosis. Punctate basophilia was not seen. A radiograph of the skull was clear ; there was no evidence of lead deposition in the long bones. The fundi were normal but were of the albinotic type. The Mantoux test and the Wassermann reaction were negative. The head circumference was enlarged to twenty inches. The cerebrospinal fluid was said to be under slightly increased pressure : this had not been measured quantitatively. There were 5 cells per c.mm., the chloride was 720 mg. per 100 c.cm., and there was no increase in protein. At that stage, the present writer, who was then asked to see the case in consultation, suggested a diagnosis of cerebral thrombophlebitis secondary to the follicular tonsillitis.

Discussion

It is perhaps significant that these cases have a number of factors in common which entitle them to be brought together as a single clinical group and justify the diagnosis of cerebral thrombophlebitis being made on purely clinical grounds without any specific evidence of an actual thrombotic lesion in the dural venous sinuses or their tributary veins These common factors are : a raised intracranial pressure with marked papillœdema ; an external hydrocephalus with the accumulation of subarachnoid fluid ; small ventricles normal in size, shape, and position ; a septic focus, usually about the head but in some cases in a remote situation ; and a tendency towards spontaneous resolution of the symptoms.

In each of these cases a blood sample was taken and examined for fibrinogen B by Mr. Lyons. As the patients have been referred at different stages in the course of their illness, it was not possible to control the results quantitatively, and no attempt was made in this early enquiry to establish any time relationships between the stage of the illness and the amount of fibrinogen B present. Lyons has pointed out that the fibrinogen B level may rise and fall rapidly during the course of an infective state, and a grade 4 result may fall to grade 1 within a few hours. The significant finding in the investigation, however, was that every case examined returned a positive fibrinogen B result, as shown in the Table. A control series of ten cases of intracranial tumour returned a negative fibrinogen B in all cases.

TABLE

SUMMARY OF FINDINGS

Case No.	Clinical picture	Infective focus	Fibrinogen B (grade)	Result
A	Vomiting papillœdema	Dental sepsis	(Not tested)	Resolution
1	Headaches; blurred vision; papillœdema	Purulent vaginal discharge	1	,,
2	Right paresis and anæsthesia; blurred vision; headache; papillœdema	Tonsillitis; antritis	3	,,
3	Headaches; focal fits; blurred vision; papillœdema	Infected varicose ulcer	4	,,
4	Diplopia; papillœdema; blurred vision	Not detected	1	,,
5	Headaches; blurred vision; papillœdema	Cholecystitis (?empyæma)	3	,,
6	Vomiting; enlarged head	Tonsillitis	3	Pending

The method of carrying out the examination for fibrinogen B is simple, and has been described by Cummine and Lyons (1947): "The reagent for the fibrinogen B test is prepared as follows. Two grammes of beta naphthol are dissolved in 100 millilitres of 50 per cent. alcohol and the solution is exposed to oxygen when it turns brown. It is not essential to aerate the reagent, but when this is done it appears to increase the rate of gel formation. One millilitre of plasma is added to 0·25 millilitre of this reagent in a 15 x 100 millimetre tube, mixed immediately, and allowed to stand for ten minutes. At the end of this period the plasma is examined for clot formation. The presence of a clot indicates that fibrinogen B is present in the plasma." The degree of the reaction is graded from 1 to 4 depending on the physical characters and intensity of the resultant clot.

Further enquiry must be directed towards the relation between the intensity of the fibrinogen B reaction and the particular stage of the thrombotic lesion, and a large series of suspected cases must be studied before the positive diagnostic merit of this test can be accepted. Cummine and Lyons have shown that circulating fibrinogen B produces rouleaux formation of red blood cells, and that by increasing platelet fragility it may liberate thromboplastin into the blood stream. Under suitable conditions of low pressure and slow rate of flow, this mechanism predisposes to intravenous thrombosis. Symonds (1937) has, moreover, pointed out the probable role of bacteræmia which may add a further predisposition through mural damage in the venous sinus or its tributary veins

If a thrombotic lesion in relation to the arachnoid granulation filters is accepted as the pathological basis for this condition, there should be little hesitation in deciding that surgical decompression will be of little help in reducing the intracranial pressure. It has been shown in the number of cases presented here that the characteristic finding is a large lake of subarachnoid fluid which is, no doubt, dammed back by the blockage of the reabsorbing mechanism. It is likely, therefore, that subtemporal decompression, which, in the presence of a space-occupying lesion, may prove effective by removing venous stasis as the result of the extra room provided, will not be effective here, where a portion of the venous system is partly or totally filled by clot and reabsorption of cerebrospinal fluid is prevented. The therapeutic attack should be directed, as soon as one has excluded a space-occupying lesion, towards removal of the infective focus, to inactivation of the circulating prothrombin in the blood by intravenous injection of heparin, to the reduction of prothrombin formation in the liver with Dicoumarol, and to decompressing the optic nerves in the case of rapidly deteriorating vision by repeated spinal drainages. The use of anti-coagulants must, of course, be controlled by a regular examination of the patient's prothrombin time, coagulation time, and fibrinogen B level.

At the present time further studies are being directed to the prothrombin and coagulation times and the fibrinogen B levels, in a series of similar cases throughout the course of the illness.

Summary

Seven cases of cerebral thrombophlebitis are described. In all six cases examined the blood revealed the presence of fibrinogen B.

REFERENCES

Cummine, Harold, and Lyons, Raymond (1947). *Proc. Urol. Soc.*, **1**, 17.
——,——(1948). *Brit. J. Surg.* (In the press.)
Martin, J. Purdon, and Sheehan, H. L. (1941). *Brit. med. J.*, **1**, 349.
——(1941). *Ibid.*, **1**, 537.
Phillips, Gilbert (1935). *Med. J. Aust.*, **2**, 289.
Symonds, C. P. (1931). *Brain*, **54**, 55.
——(1937). *Ibid*, **60**, 531.
——(1940). *Brit. med. J.*, **2**, 348.

EPILEPTIC RESPONSE TO PERIPHERAL INJURY

BY

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From a study of the literature it is apparent that in certain cases of reflex epilepsy there is an association between the epileptic response and peripheral injury. About one hundred years ago there was a woman who suffered from generalized epileptic convulsions. Her left arm had been amputated at about the middle of the humerus, and she later complained of localized convulsions in the stump. Hancock (1852) removed a large neuroma from the stump with only temporary alleviation, and he later had to remove the limb at the shoulder joint, but two months later the shoulder muscles around the scar became convulsed.

The probing of an infected sinus of a femur (Parker, 1887), or the stretching of a traumatized sciatic nerve (Hadden, 1887), were followed by seizures. Critchley (1933) described a patient who had a typical epileptic attack whilst a dressing was being applied by her doctor to her burnt arm. She had never before had a fit, but her child was an idiopathic epileptic. Mitchell and Spiller (1904) described two such cases. The first, a soldier in the American Civil War, had been wounded in the sciatic nerve, and the second, another soldier, had had his arm amputated. Both of these patients developed continuous movements in the stump of the affected limb which, when restrained, were followed by more generalized convulsions.

Holmes, in his Savill Memorial Oration for 1927, related that whilst he had been studying the disturbances of sensation produced by cortical lesions he had found, during prolonged examination of tactile and other forms of cutaneous sensibility over one hand, that Jacksonian spasms occasionally began in this part in patients with cortical lesions who were not subject to frequent attacks. Indeed some patients were reluctant to submit to examination when they realized the connexion. He considered that the most effective stimulus was light touch with a camel-hair brush.

Feiling, in his Lettsomian Lectures for 1942, also recorded the connexion between epileptic convulsions and peripheral nerve injury. He had found that in a few cases of this kind the attacks began by abnormal sensations arising in the injured area, which often spread to involve the whole of the same side of the body and which in some instances culminated in a generalized fit. He had observed a soldier who had been wounded in the right elbow in the 1914 war and whose arm had been amputated. About twelve years later the sensory attacks started. These consisted of slight twitchings which arose in the stump and spread after a while to the right side of the face, trunk, and leg. Two or three years later the convulsions spread to the opposite side of the body, and when this occurred consciousness was lost. Handling of the amputation stump did not act as an excitant to the attack.

Apart from Holmes's cases (1927), where a cortical lesion had caused the disturbed peripheral response to a specific and effective stimulus, little is known of the nature of the abnormal physiology of reflex epilepsy. Because of this it would seem to be worth while to record any case in which something is known about the relationship of an abnormal peripheral mechanism to epileptic fits. The following case is therefore described in some detail as it presents evidence of abnormal cortical function together with peripheral nerve injury, both of which abnormalities were acquired before the occurrence of the patient's first epileptic fit, in which the nature of the sensory precipitant and its site of action were constant.

Case Report

H.M. was an unmarried van driver aged 41 years. He came from healthy stock, and no history of fits or migraine could be elicited. He had had no serious illness until he contracted malaria in 1930, whilst abroad in the Army, and four years later, whilst still in India, he had been treated for tape-worm infestation. He was

again treated for a recurrence of this complaint in 1940. He had "spinal meningitis" in 1940, which was cured in seven weeks. Little is known of the exact nature of this illness, but there have been no sequelæ and he remained well for the next six years. On Jan. 27, 1947, he accidentally crushed his left hand beneath a two-hundredweight cable drum. This produced a cut on the dorsum of the left hand, about an inch long, at a level of the bases of the second and third metacarpal bones, and this was deep enough for him to be able to see his tendons. He noticed shortly afterwards that the whole of the thumb, the dorsum of the index finger, and outer half of the middle finger seemed numb; clinical examination later showed that this numbness was due to local damage to the terminal cutaneous branch of the radial nerve.

It was about twenty-four hours later that, while sorting some papers, he noticed that these seemed to tickle his left thumb and index finger in a curious way, which description he could not amplify except that it felt quite pleasant to him. This was followed suddenly by stiffening of the thumb and first two fingers. The thumb was adducted into the palm, then the fingers flexed at the metacarpo-phalangeal joints. Within a second or two of this happening the whole arm began a series of jerking movements, the elbow became flexed and the arm rose to a position of abduction at the shoulder until it formed an angle of 90 degrees with the trunk. The fit lasted for about half a minute, but recurred two or three times a day for the next week, being provoked by only mild and light stimuli. He found that knocking or hurting his hand did not act as a trigger. Owing to the position of abduction which the arm assumed, he became very self conscious, and tried by gripping his knee with his hand to restrain the limb. He found, when he did this, that the embarrassing abduction could be avoided and also that the limb would "cool down" quicker, and that the episode would be much milder.

About ten days after the injury he was sorting some requisition slips in his van when he suddenly appreciated that the curious tickling sensation produced by the papers on his left hand was spreading up his left arm. He gripped his knee tightly, but the feeling continued to spread, his jaw became clenched and he felt that his face was twisted. This was followed by a steam-engine-like noise in his head and he lost consciousness. He recovered in about twenty minutes, felt confused, and found that he had bitten his tongue.

He was examined about three weeks later at the National Hospital for Nervous Diseases, Queen Square, London, and no abnormal physical signs were found except for an area of blunting to pin prick over the dorsum of the left thumb and the index and outer half of the middle fingers corresponding with part of the area supplied by the terminal part of the superficial branch of the radial nerve. On April 28, 1947, he was admitted to the hospital for investigation under the care of Dr. Denis Williams. Radiograph of the limb muscles demonstrated the presence of calcified cysts. Although no abnormal calcification could be seen within the skull, the cerebrospinal fluid was abnormal. It was clear, contained 46 cells per c.mm., 18 polymorphs, and 28 lymphocytes, and 50 mg. of protein per 100 c.cm. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The electro-encephalogram showed no physiological dominant frequency, and there was persistent low voltage fast activity in all leads with no focal origin. There was no sign of any local disorder and the curves were symmetrical. A diagnosis of cerebral cysticercosis was made and he was discharged from hospital with a prescription of Tab. phenobarbitone, gr. ½ three times a day, which dosage was sufficient to prevent any further seizures during the next eight months.

The next examination was made at St. George's Hospital, London, on Oct. 24, nine months after his injury, and except for some impairment of appreciation of pin prick over the back of the outer three digits, which extended along the outer side of the index finger, there were no other abnormal physical signs. He had not taken any sedative for four days before the appointment. Electro-encephalographic investigations were then carried out. With the patient lying at rest, records were taken with a Grass 6 channel apparatus. The alpha rhythm was of low voltage, very unstable, and of a frequency of 10 to 12 c/sec. Continuous low voltage fast activity at 18 to 22 c/sec. was present in all leads, but was best seen in both parietal regions. The records were quite symmetrical, there was no evidence of any focal abnormality. There was no abnormal response to overbreathing. The electro-encephalogram was then recorded while various surprise stimuli were applied to the area of impaired sensation on the patient's left hand and also, so as to serve as a control, at a different time to the corresponding area on the right hand. The patient was not informed of the nature of the stimuli nor when they would be applied. The period of stimulation lasted for about one minute in each case. First the effect of tickling lightly with cotton wool was tried. He remarked afterwards that this felt very different on the two hands, that on the epileptogenic zone being "pleasant," whilst that on the control area was "just ordinary." Next a slightly heavier touch with cotton wool was applied, then slowly repeated rhythmic pin pricks, showers of rapid pin pricks, and sudden very loud noises. Finally he was given some slips of paper which he fingered and rustled in both hands. Careful study of the electro-encephalographic records showed that not one of these various stimuli produced the slightest change in the curves suggestive of epileptic discharge, and except for a few artifacts the records were unchanged.

He remained symptom-free, continuing to take Tab. phenobarbitone gr. ½ three times a day, until Christmas morning, 1947, when, as he was screwing up some newspaper with which to light a fire, he produced the aura in the left thumb and first finger. He swore loudly, gripped the fender as hard as he could, and thus aborted the attack. He had another minor focal seizure that afternoon, but he does not remember what the trigger was on that occasion. That night he played cards with three friends. Early in the game he was dealing the cards with his right hand and at the same time was pushing the cards forward from the pack, which he held

in his left hand, on to the lateral side of his index finger. This produced the usual aura which on this occasion proceeded to a major fit. Since then the dosage of phenobarbitone has been increased to gr. 1 three times a day and there has been no recurrence of fits. About the beginning of February, 1948, he observed some tape-worm segments in his stools. He was therefore treated with filix mas, but a careful search of the stools did not reveal the head of the tænia solium. Two weeks later he was treated with carbon tetrachloride and oil of chenopodium, again without success.

A further neurological examination was made on March 31, 1948. No abnormal physical signs were found, and sensation in the left hand was apparently normal. Another electro-encephalographic examination was carried out, and the experiments of the previous examination were repeated. He was also lightly stroked with a camel-hair brush for fifteen minutes on the left index finger, during which period he overbreathed for six minutes, but as before there was no change in the character of the electro-encephalographic records.

Discussion

After careful analysis of cases of this type, and study of the experimental work which has been performed, it is only possible to speculate on the mechanism of the production of this kind of epileptic response. It is possible that in those cases associated with peripheral injury there may be some abnormality in the reflex arc on the afferent side between the periphery and the cortex. Holmes (1927) refers to Sauerbruch, who had passively moved a monkey's paw for a long period. After such exercise, injection of cocaine in a previously ineffective dose produced a spasm of the limb. Clementi (1931) applied strychnine near the uncinate gyrus of a dog, after which fits could be provoked by olfactory stimulation with pungent substances. Muskens (1928) quotes Amantea, who applied strychnine to the motor centre of an extremity, after which painful stimulation of the limb resulted in a fit.

Denny-Brown and Robertson (1934) in a very intensive study of local epileptic convulsions which they carried out before the electro-encephalogram was used in epilepsy, put forward the hypothesis that the fundamental epileptic process is continuous and widespread, and in its lesser intensities productive of outward effect only by coalition with other intense nervous processes, and that the added stimulus is related solely to its power to cause a sudden increase in excitability in the patient concerned. The electro-encephalogram does in fact show that external stimuli can alter the rate and rhythm of the waves. For instance whilst an electro-encephalogram is being recorded the effect of the opening of the eyes is frequently observed. As a rule the alpha rhythm is blocked when the eyes are open, but when the eyes are shut the alpha rhythm resumes immediately. It is a not infrequent finding in patients with idiopathic epilepsy that a burst of epileptic activity, generally in the form of a spike and wave, occurs as soon as the eyes have been shut to command. In a series of abnormal epileptic electro-encephalographs recorded at St. George's Hospital 9 per cent. exhibited this phenomenon. Goodkind (1936) and Robinson (1939) have both reported sensory precipitation of this kind. Shaw and Hill (1947) investigated a case of musicogenic epilepsy and produced evidence on the electro-encephalogram to show that there was a constant pattern for the development of the fit. No change of rhythm was seen while music was played before the fit began, and the cortical discharge did not begin until six or seven seconds after the clinical onset. Dawson (1947) described a subject in whom sensory stimulation, in the form of stretching a muscle or electrical stimulation of a peripheral nerve, provoked myoclonic seizures. He showed conclusively that a peripheral stimulus caused an afferent volley which resulted in an electrical change of potential over the contralateral scalp. Thus stimulation of a leg was followed by a response near the mid-line, or 6 to 8 cm. lateral to it, when the arm was stimulated. He concluded that these responses to stimulation are cerebral in origin.

In the case here described the actual nerve injury did not serve as a noxious stimulus to the reflex, nor did the ordinary sensations of pain, pressure, touch, etc., act as excitants, but in his case a light tickling touch applied to the area supplied by the injured nerve resulted in about twenty focal fits, two of which progressed to major attacks with convulsions. It seems that the stimulus of light touch was altered as the result of the peripheral nerve injury and that it served to detonate a focal cortical outburst. It is remarkable that the epileptic fits should have started so constantly in that exact part of the body which had been injured, and that it always required the same type of stimulus to release the trigger. Although the incidence of the fits was most frequent in the first few days after the injury, and very infrequent since, he has for the greater period of the time been receiving a regular dosage of Tab. phenobarbitone, so the healing of the peripheral nerve injury is not necessarily the only reason for the improvement.

It is of interest to note that, in this case, the stimulus which acted as a trigger was of a very similar type to that which was found by Holmes to provoke the epileptic responses in his cases. He had also remarked upon the fact that with stimulation the clonic movements start almost invariably in the part that was being tested. Holmes

considered that there was evidence that stimulation of a limb, which is subject to motor or sensory epilepsy, or of a sense organ to which analogous phenomena are referred, may excite epileptic symptoms if the corresponding part of the cortex is in an unstable state. Dawson (1947) has, by electrical means, been able to confirm this concept which Holmes had reached by clinical observation.

Summary

A case of symptomatic epilepsy is described where the fits were precipitated by the passage of a specific sensory stimulus through an injured peripheral nerve.

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References

Clementi, A. (1931). *Arch. Fisiol.*, **30**, 1.
Critchley, M. (1933). *Ann. Rep. Lond. Co. Council*, vol. 4, part 3, p. 133.
——(1935). *Schweiz. Arch. Neurol. Psychiat.*, **35**, 256.
Dawson, G. D. (1947). *J. Neurol. Neurosurg. Psychiat.*, **10**, 141.
Denny-Brown, D., and Robertson, E. G. (1934). *J. Neurol. Psychopath.*, **15**, 97.
Feiling, A. (1942). *Trans. med. Soc. Lond.*, **63**, 178.
Goodkind, R. (1936). *Arch. Neurol. Psychiat., Chicago*, **35**, 868.
Hadden, W. B. (1887). *Brit. med. J.*, **1**, 510.
Hancock, Mr. (1852). *Lancet*, **1**, 281.
Holmes, G. (1927). *Ibid.*, **1**, 957.
Mitchell, S. W., and Spiller, W. G. (1904). *Trans. Assoc. Amer. Phys.*, **19**, 433.
Muskens, L. J. J. (1928). "Epilepsy." London.
Parker, R. W. (1887). *Proc. med. Soc. Lond.*, **10**, 85.
Robinson, L. J. (1939). *J. Nerv. ment. Dis.*, **90**, 333.
Shaw, D., and Hill, D. (1947). *J. Neurol. Neurosurg. Psychiat.*, **10**, 107.

PSYCHOLOGICAL EFFECTS IN DEPRESSIVE PATIENTS OF THE MARIHUANA HOMOLOGUE SYNHEXYL

BY

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The search for drugs to combat psychiatric symptoms, especially depression, has a long history. Because of the close association, particularly in the sufferer's mind, between pain and mental anguish, the opiates have often been used for alleviating such symptoms. Hashish, likewise, for long known to produce pleasant, dreamy states, has been used at times, and a very recent example of its recommendation is for the reducing of anxiety and tension in patients with duodenal ulcer (Douthwaite, 1947).

Interest in the chemistry of hashish, or marihuana as it is usually called in America, has recently led two or three groups of workers—Todd (1945) in Cambridge, and Adams (1942) and Loewe (1944) in the United States in particular—to investigate various compounds isolated from it. They have also prepared homologues of the natural products, and of these synhexyl showed the most promise of being useful as a euphoriant. It has become available for clinical trial, and Stockings (1947) recently published a report on its favourable effects in alleviating depressive mental states in fifty patients, more than half of whom were chronic mental hospital inmates. The investigations to be reported here were on a smaller group of patients—fourteen—who were intensively studied with a view to gaining a clear picture of the effect of the drug and its value in the treatment of depression.

Method of Investigation

The patients were examined in groups of two or three at a time. Except for the earliest group of three patients, on whom subsequent dosage was standardized, and who exhibited mainly depersonalization in a setting of depression or hysteria, they were all in patients selected because of a predominant clinical picture of depression. All were voluntary patients, and able to co-operate fully in the investigation.

The examination of the effect of the drug was carried out by means of clinical study throughout the period of its effect, by simple psychological tests, to be detailed below, and by introspective reports in answer to certain standard questions. In order to sharpen the clinical impression a comparison with benzedrine was made. The total period of study of each group of patients lasted four days : a control day with clinical examination and a short rehearsal of the psychological tests given without any drug ; a second day beginning with 30 mg. synhexyl at 9 a.m. ; a third with 20 mg. benzedrine at 9 a.m. ; and a fourth with 40 mg. synhexyl at 9 a.m. Tests were carried out at 9 a.m. before any drug effect had occurred, at 1.30 p.m. when the action was usually at its height, and at 3.30 p.m. when the action was wearing off. These four days were not necessarily consecutive but were usually all within one week, and the order of the giving of the drugs was always the same. In the earliest groups, tests were also made at 11.30 a.m., but these yielded no significant differences when compared with the findings at 1.30 p.m. and 3.30 p.m.

The General Clinical Picture

About two hours after the ingestion of synhexyl, there was a sudden onset of drowsiness and lightheadedness, spontaneously described by several subjects as like the early states of intoxication by alcohol. The sensation might pass off in a few minutes, but it then recurred in waves of increasing depth and length, the maximum effect being obtained from three to five hours after taking the drug. What might be described as a " pre-intoxicated " stage occurred in most patients with the smaller dose of synhexyl. The characteristics of this period were related closely to the underlying personality, and are discussed later. In general the subjects showed an increase in apprehension and a clear subjective awareness of lack of being master of themselves, leading in some to a pleasant lackadaisical state, and in others to a more definitely unpleasant increased preoccupation with the fears and worries of their depressive condition. With larger doses the clinical picture became more uniform again, as

the subjects passed into a state of slight but definite impairment of consciousness which might be accompanied by very marked drowsiness. Sleep was light and accompanied by dreams. The exhibition of the drug to patients in groups showed clearly that there was an increase in suggestibility, for the symptoms of all the subjects in any one group tended to be similar to each other, but to differ from those of another group. For example, the members of one group stressed their sensation of drowsiness, while in another group a fatuous euphoria was conspicuous. Symptoms passed off in about six to eight hours and left no sequelæ, except in one hypochondriacal patient who has continued to complain that the drug has increased her various symptoms.

Appetites were described as ravenous by several subjects. At the height of the intoxication an irregular tremor of the outstretched hands was common, combined with a tendency to sway in the Romberg test. The hands were cold and clammy, but no unusual vasomotor disturbances were noted. The pulse rate, taken half-hourly throughout the day, showed no consistent raising or lowering.

Details of the Clinical Picture and Their Relation to the Personalities of the Subjects

Disturbances in Perception and Sensation.—The commonest and most marked changes occurred in somatic sensations. In four subjects depersonalization had been a marked feature of their clinical state, and in all of them the symptom was made worse with synhexyl. Although intensified, the characteristics of a particular subject's feelings of depersonalization did not differ when the subject was under the drug from such characteristics when the subject was not under its influence. Other somatic sensations were those commonly associated with anxiety: palpitations, " tight band round the head," " something in the throat," " trembling in the knees." Five out of the eight patients who showed no depersonalization reported these somatic sensations. For most of the patients they were very unpleasant, and they occurred whether or not the subject had previously had marked anxiety symptoms.

Changes in auditory perception were not reported, but three patients spoke of mild visual disturbances: things looked darker, or dead. One patient (Case 1) reported definite disturbances of time perception. " Time seems unreal. Things keep surprising me, it's like coming out of gas. It's as if everything were a long time ago."

Case 5.—One patient had a form of hypnogogic experience. She was married and aged 33. Her mother was a domineering strict woman who had remarried after the death of the patient's father when the patient was aged 3. There were step-sibs only. From the age of 5 to 8 years the patient had as a companion a girl cousin who died later, and then for long periods she lived with an aunt and a grandmother. She was a solitary, delicate child with many fears and worries, who never let herself go, and was excessively conscientious but only average at school and clerical work. There was a history from the age of 15 of several attacks of fears, mainly of tuberculosis (which had been suspected in her as a child). The present attack was longer and deeper, with a depressive effect and many obsessional fears and thoughts, mostly about the health and life of her husband and one child.

After taking 40 mg. of synhexyl she recounted an interesting vivid hypnogogic experience which she stressed as being more vivid than a dream: " When I dozed off my thoughts seemed to rush back into the past, and I imagined I was going somewhere as I did as a child, down a street in which I lived from the age of 7 to 12 years. I was unhappy because I was sent there for my health and my cousin and step-brother had both died in that street." (This street is near her present home and even now she refuses to walk down it although she thinks of its connexion with her previous life only when she has to pass it.)

The synhexyl made her feel giddy and depressed, and she had palpitations and a drawing feeling at the back of her head. At the height of the drug effect she tended to giggle rather feebly but denied she felt particularly happy. There was no increase in her obsessional thoughts. Benzedrine gave her " a lovely feeling of happiness," and she felt as if she could do things without so much worrying.

This is an interesting example of a person who in childhood was obsessed with many affect-laden thoughts and imaginations which synhexyl allowed to emerge again in semi-consciousness.

Disturbances in Thought Processes.—Some mild degree of lack of concentration was noticed in all subjects, and marked thought disturbances occurred in two or three patients. All of them were aware of the changes but were inaccurate in their estimate of how they were doing on the psychological tests. Several patients (Cases 1, 5, and 10) had histories of obsessional thinking and habits, but this thought disturbance was not seen at all under synhexyl in these or other patients. The following is an example of a fairly marked thought disturbance.

Case 6.—The patient (Case 6) was aged 26. Her mother was hypochondriacal, her father irritable and bad-tempered. She was the youngest of three, being of normal birth and development, and described as a gay girl with plenty of admirers, but much spoiled and very dependent. As a wife she was suspicious and nagging, constantly accusing her husband of infidelity. Her build was asthenic, her personality markedly schizoid. Over some months anxieties and phobias about food had developed, together with obsessional washing rituals, fears of pregnancy, and many hypochondriacal ideas.

Under the influence of 40 mg. synhexyl she showed a peculiar schizophreniform reaction : a few minutes after she had completed the designs test she returned to tell me that she had been listening to symphony music on the radio, " It seemed the only real thing at the time. My husband says I don't like classical music, but he's fond of it and thinks I don't understand it. I feel as if I've completed a picture, not only in the designs but as a person. I feel it is this place really, my husband and child are outside, I am shut away from them in here." She appeared strange, abstracted, preoccupied, and stared vacantly ; she easily burst into tears without any great underlying affect. Later when questioned she was rather giggly. " I really felt as if I had completed a picture with the designs—I suppose it is the idea of the drug to clamp down on you and now I've finished with them." On benzedrine she wanted to sing and felt " as I am sure I normally am. I realize what a disagreeable person I must have been to other people." Her appetite remained good. She was discharged from hospital a few weeks after the trial of synhexyl but little improved. During follow-up in the out-patients' clinic her symptoms remained much the same, with the addition that she blamed the synhexyl now for many of her peculiar feelings and thought disturbances.

Disturbances in Feelings and Emotions.—The relation between the clinical picture and previous personality is here closest ; both in the nature and quality of the affect and in the degree to which the subjects were disturbed. The most labile and immature personalities showed the most marked affective changes, and the picture was in their case the most remote from their normal (pre-morbid) affective state (Cases 1 and 5). On the other hand cases whose patterns of personality breakdown were more fixed showed a picture like their usual, differing only in being more exaggerated in some cases, as is shown, for example, by Cases 2 and 9.

Case 2.—A woman aged 73 had a normal birth and development, but had an unhappy home owing to her mother's remarriage to a chronic alcoholic. She secretly married a Frenchman, and for most of their married life they lived apart in their respective countries. In spite of this she has carried on, a quiet and stable woman, rearing several children, until at the age of 71 the slow onset of depression without any evidence of intellectual deterioration. Investigation of recent stomach pains and indigestion revealed an incidental carcinoma of the stomach. Her reaction to 30 mg. synhexyl was to feel just tired with some slowing of thought. The bigger dose produced more definite nervousness and giddy feelings. Objectively she appeared but little changed, perhaps a little shakier in handwriting and rather easily confused in the psychological tests. With benzedrine she felt better and not so nervous but there was little objective change.

Case 9, aged 44, was the daughter of a clergyman-schoolmaster, a rather anxious person who has probably suffered from depressive episodes. One brother suffered from postoperative depression, another committed suicide. She developed normally at school and university and she now holds a professional qualification and has been doing well, though not brilliantly. She has had two unhappy love affairs. In the past two years she has had four periods in hospital with acute depression, and more than one attempt at suicide. She appears to have been a chronically anxious, worried, introspective person with little self-confidence and self-insight. Synhexyl was given when the patient had somewhat improved after four therapeutic electrical convulsions. On the smaller dose she began to feel " giddy and muzzy, a pleasant feeling if one hadn't anything to do." In manner she appeared a little elated and hearty. With 40 mg. she felt very sleepy and faintly giddy " rather like the first stages of intoxication "—though " drinks " normally make her " chatty " which was not a feature of her reaction on this occasion. On benzedrine she felt " quite full of beans and not sleepy as yesterday."

Although under the influence of synhexyl many of the patients were " giggly," given to making feeble jokes and laughing immoderately at very little, the prevailing affective response was one of apprehension, and in retrospect only two patients said the sensation was at all enjoyable (Cases 9 and 3). Case 3 was the only one in whom any real clinical improvement followed administration of the drug.

Case 3.—A woman aged 40, was the daughter of a street trader. She had a normal birth and development but was always considered highly-strung and excitable. She married at 23 and has one child aged 16. Her husband is dull, irresponsible, and often out of work. The patient has had much worry and responsibility, which she has succeeded in carrying competently, until her first breakdown after the birth of her baby sixteen years ago. A second breakdown in 1945 was precipitated by a blood transfusion. She had several anxiety attacks resembling faints, and when drowsy she had sensations of falling and of whispering voices. At the time of this breakdown she was admitted to hospital. She was mildly confused from a self-administered overdose of barbiturates ; but this state cleared up, leaving a depressed, emotional, agitated picture. She improved, but soon relapsed on return to her unsatisfactory social condition, and she returned to hospital a few months later. The symptoms on this occasion were more dramatic. Whispering voices, and faces grinning at her as night fell, were prominent hypnogogic symptoms. She was histrionic in general behaviour and preoccupied with her wickedness and guilt. Before synhexyl was given she had had a course of modified insulin treatment with improvement, marked especially by the disappearance of the hypnogogic hallucinations. She became a popular member of the ward and a sympathetic listener to other patient's troubles, although in relation to the doctor she was still full of her own. At 1.30 p.m. on the day when 30 mg. synhexyl was given she said, " I feel worried because I can't worry over anything." Later that afternoon she said " For the first time for a long time I feel comfortably tired." She had—and this was unusual for her—been lying on her bed in the afternoon. She was asked to close her eyes, but no

hypnogogic imagery was called up. She remarked that the "faces" only occurred at night. After the larger dose of synhexyl she felt even more comfortable and drowsy, "living in the clouds"; but the next day she wrote, "In the early evening (of yesterday) I felt kind of anxious and panicky, afraid to think and wanted to keep on pushing my thoughts away, thankful to go to the social to help stop myself giving way to doubts and fears again and that feeling of mistrust. I slept much better during the night."

In view of the improvement she was given 20 mg. synhexyl twice daily and remained happy and comfortable for some days. She went home for the week-end, back to the same old difficulties; and in spite of continuing to take her tablets she relapsed and returned to her former condition. However, she said she felt sufficiently encouraged "to try again," so she left hospital, but when seen in the out-patients' clinic she was in much the same state of agitation as before.

This patient is also of interest in being the only one made definitely worse with benzedrine. "I've a horrible feeling I'm not doing so well as I should, everything is an effort." It began just before lunch when she did not want to eat and could not be bothered with anybody. Since 11.30 a.m., two-and-a-half hours after the drug, she developed spasms of shivering, feeling cold in her head and body, and needed a hot drink and extra jacket. She wanted to keep on doing things "to hang on to myself. I don't feel as though I'm here." She denied ever having had such feelings before.

Disturbances in Consciousness.—With the larger dose of synhexyl nearly all the patients showed some clouding of consciousness. Several said they felt strange and floating in and out of the world. Giddiness, remarked on by half the subjects, fluctuated in intensity during the course of the drug effect. Five patients were markedly drowsy, and dozed in the afternoon, contrary to their usual custom. Case 3 enjoyed the lightness and vagueness of the cloudy state; but the others, who did not take refuge in sleep, were disturbed by the unsteadiness it brought about.

Case 1.—This patient, aged 24, is the daughter of a dentist and a domineering histrionic mother. There is a history of insanity on the father's side. She was a premature baby but developed normally and did well at school. She began a medical career, getting only as far as the beginning of the anatomy course. Since then she has had various jobs closely related to home. She is a generally immature, dependent, querulous girl with a history of various obsessional phenomena in her teens. Presenting symptoms were mild anorexia nervosa and a tendency to vasomotor rhinorrhœa, a fear of "hay-fever" being prominent in her mental state. Physical immaturity was quite marked, especially in the development of the breasts and hair. After 30 mg. synhexyl she said, "I feel absolutely terrified, and frightened for my sanity." She looked depressed and worried, her thoughts moved more slowly, concentration was difficult, and she felt generally remote and drowsy, when not anxious. She felt she had improved in the mental tests, which was not so. With 40 mg. synhexyl she felt remote and dazed. "I kept drifting off and coming back into the conversation. It is as if everything was a long time ago. When I left the dormitory for a moment and then returned I was surprised to find they were still talking about the same thing. Things don't seem joined together. I have to concentrate on being here. I can see now the Ward Sister coming in to tell me to come to see you here, it's in my mind, not a delusion."

She said she felt happier than with 30 mg. of synhexyl, "but to-day I am so gone out that I don't sort of feel anything." In her manner she appeared the most intoxicated of all the subjects, markedly unsteady on her feet, grinning and giggling fatuously, hardly able to co-operate on the tests. The relatively severe reaction to synhexyl is clearly related to her poor previous personality, which easily crumbled with any stress. It is interesting that no obsessional symptoms were noted. Her appetite was "ravenous," anorexia being the only symptoms which could really be said to have improved. On benzedrine she felt happier and brighter, she sought out people to talk to, and in the test situation she was more outgoing, talked louder, and smiled more.

Disturbance in Conation and Will-Power.—This needs only brief mention as it will be discussed in relation to the persistence test. All subjects showed a decreased interest in work and were content to doze or sit about. They found their attention wandering from the psychological tests.

Psychological Tests

The Battery of Tests.—The battery of tests given consisted of:

An adding test (of the old Kraepelinian variety).—In this the subject has to add together groups of two single digits, writing down only the second digit if the total is more than 10—e.g., $6+3=9$; $8+9=7$. The numbers are arranged in columns and the subject adds continuously for five minutes, drawing a line at the point he has reached when the examiner calls every thirty seconds. In this way a work curve is obtained of six consecutive thirty-second periods of addition.

A perseveration test (taken from Cattell's (1946) battery).—The three sub-tests chosen were those with the highest factor saturation: that is, writing the subject's own name forwards and backwards, writing three digits forwards and backwards, and a five-letter word forwards and backwards for one minute in each direction. A new combination of digits and a different word was used for every test occasion. The score is the ratio of words or letters written forwards to those written backwards.

A concentration test (adapted from one being investigated by Dr. Eysenck).—The examiner reads out a string of random numbers and at irregular intervals calls "Now." The subject then has to remember the preceding two numbers called out. "Now" is called out four times, and at the last the subject has to write down all eight numbers he has been expected to remember.

TABLE I

ADDING TESTS: TOTAL FIVE-MINUTES SCORES

Drug and dose	Time	Case									Average
		1	2	3	4	5	6	7	8	9	
Synhexyl 30 mg.	9.00 a.m.	102	65	108	104	72	84	96	125	166	102
	1.30 p.m.	89	53	83	108	100	113	108	117	172	105
	3.30 p.m.	111	59	91	117	114	116	112	136	167	108
Benzedrine 20 mg.	9.00 a.m.	145	67	67	86	115	145	—	164	204	124
	1.30 p.m.	136	63	72	98	138	164	—	178	203	132
	3.30 p.m.	—	—	—	—	148	155	—	—	—	—
Synhexyl 40 mg.	9.00 a.m.	118	74	70	143	154	171	118	158	197	134
	1.30 p.m.	107	62	48	140	152	144	110	133	184	120
	3.30 p.m.	105	84	47	138	159	149	114	198	198	132

TABLE II

PERSEVERATION SCORES FOR FIVE-LETTER WORD: RATIO FORWARDS/BACKWARDS

Drug and dose	Time	Case									Average
		1	2	3	4	5	6	7	8	9	
Synhexyl 30 mg.	9.00 a.m.	4·2	7·5	6	4·6	6·8	5·4	7	8	6·8	6·1
	1.30 p.m.	6·8	11	5·3	6·8	5·2	4·8	6	4·5	8·5	6·5
	3.30 p.m.	4·3	6·5	6	6·8	4	7	4·5	3·3	9	5·9
Benzedrine 20 mg.	9.00 a.m.	4	5·3	7	7·5	6	6·2	—	3·7	4·3	5·5
	1.30 p.m.	5	15	7·5	8·7	4·5	5·3	—	4·6	5·3	7·1
	3.30 p.m.	—	—	—	—	7·8	6	—	—	—	—
Synhexyl 40 mg.	9.00 a.m.	3	5·7	4·4	5·0	3·7	6	5·8	5·7	4·7	4·9
	1.30 p.m.	3·8	3·7	4·4	5·2	5·8	8	3·6	3·9	5·1	4·8
	3.30 p.m.	4·3	7·5	6	5·8	8	4·3	5·2	4	5·3	5·6

TABLE III

CONCENTRATION TEST (SUM TOTALS OF FIGURES AND LETTERS RECALLED)

Drug and dose	Time	Case									Average
		1	2	3	4	5	6	7	8	9	
Synhexyl 30 mg.	9.00 a.m.	16	3	14	12	15	14	12	14	14	12·3
	1.30 p.m.	15	3	12	13	13	10	5	5	14	10
	3.30 p.m.	15	5	15	11	13	4	6	6	9	9·3
Benzedrine 20 mg.	9.00 a.m.	16	9	12	16	15	13	—	6	16	12·9
	1.30 p.m.	15	8	13	13	13	12	—	9	13	12
	3.30 p.m.	—	—	—	—	14	10	—	—	—	—
Synhexyl 40 mg.	9.00 a.m.	15	9	14	16	19	7	9	6	16	12·3
	1.30 p.m.	13	8	9	9	10	8	11	5	16	9·9
	3.30 p.m.	14	16	14	11	14	13	13	2	10	11·8

N.B.—Cases 5 and 6, tested together, proved to score full marks when required to remember eight letters and eight figures. Their scores, therefore, are the number of figures and letters remembered out of ten letters and ten figures.

TABLE IV

LENGTH OF TIME TEST

Drug and dose	Time	Case									Average
		1	2	3	4	5	6	7	8	9	
Synhexyl 30 mg.	9.00 a.m.	32	30	35	41	29	34	31	24	30	32
	1.30 p.m.	35	29	49	36	35	29	35	15	42	34
	3.30 p.m.	29	26	30	33	25	33	32	13	32	28
Benzedrine 20 mg.	9.00 a.m.	35	24	36	35	29	33	34	16	29	30
	1.30 p.m.	34	30	28	37	—	33	—	15	31	26
	3.30 p.m.	—	—	—	—	—	29	—	—	—	—
Synhexyl 40 mg.	9.00 a.m.	32	—	29	40	29	34	38	14	33	31
	1.30 p.m.	28	30	28	36	31	29	28	10	36	28
	3.30 p.m.	30	25	36	36	24	29	27	13	29	27

TABLE V

TIME OF LEG-RAISING (PERSISTENCE TEST) (IN SECONDS)

Drugs and dose	Time	Case									Average
		1	2	3	4	5	6	7	8	9	
Synhexyl 30 mg.	9.00 a.m.	930	54	20	38	130	115	107	30	78	167
	1.30 p.m.	280	30	17	30	35	93	65	53	56	73
	3.30 p.m.	165	64	20	34	108	285	82	65	43	96
Benzedrine 20 mg.	9.00 a.m.	1500	100	34	30	186	930	67	48	93	332
	1.30 p.m.	770	88	28	35	—	1445	—	60	56	366
	3.30 p.m.	—	—	—	—	195	590	—	—	—	—
Synhexyl 40 mg.	9.00 a.m.	930	108	33	44	120	1060	45	34	90	274
	1.30 p.m.	345	42	20	30	100	435	46	26	30	119
	3.30 p.m.	405	44	38	31	95	505	26	34	60	137

TABLE VI

TIME OF BREATH-HOLDING (IN SECONDS)

Drug and dose	Time	Case									Average
		1	2	3	4	5	6	7	8	9	
Synhexyl 30 mg.	9.00 a.m.	84	28	8	24	38	47	30	23	30	35
	1.30 p.m.	60	29	8	31	23	35	40	25	29	31
	3.30 p.m.	63	25	11	35	44	30	35	28	36	34
Benzedrine 20 mg.	9.00 a.m.	64	22	10	35	41	32	34	37	36	34
	1.30 p.m.	75	22	12	35	—	37	—	20	31	33
	3.30 p.m.	—	—	—	—	44	46	—	—	—	—
Synhexyl 40 mg.	9.00 a.m.	46	22	8	40	31	47	31	16	33	30
	1.30 p.m.	75	28	10	30	40	33	28	13	37	33
	3.30 p.m.	73	30	17	37	32	44	25	13	24	33

Length of time test.—The examiner makes two taps on the table five seconds apart and asks the subject to tap out the same interval of time. The subject has to tap out six consecutive five-second periods, so that in this way any tendency to increase or decrease of time length is magnified.

Designs test.—This was more in the nature of an experiment. In organic disturbances, as has been pointed out by Mayer-Gross and Guttmann (1936), there is a difference between spontaneity and poverty of ideas which the ordinary fluency tests would confuse. The following test was devised by Dr. Guttmann in the hope that some distinction might be made between total productivity and the quality of the productions. The subject is given six wooden blocks of different colours and flat shapes (for example, red triangles, blue rectangle, black parallelogram) and in two minutes she has to make as many *new* designs as possible. The total number of designs was considered to be related in some ways to spontaneity, and the character of the designs, such as tendencies toward making them stereotyped, etc., related to " poverty of ideas."

Persistence tests (as worked out by Dr. Eysenck, 1947).—In the first the subject has to hold her leg outstretched just above a chair seat for as long as possible without holding it with her hand or otherwise supporting it. The score is the length of time until the leg drops on to the chair. In the second the subject has to hold her breath for as long as possible.

Several other tests were tried out with one or two groups, such as other fluency tests (rhymes to a given word, etc.) and cancellation tests, but they yielded such irregular results as would be useless for investigation of the drug effect. The main difficulty encountered in devising suitable tests arose from the subjects' having to do them so many times—three times a day for three or four days—that learning and general practice effects dominated the changes in scores.

Results of the Psychological Tests.—Table I shows the total scores of the five-minute adding periods. Comparison of the 9 a.m. scores shows that marked improvement with practice occurred in most subjects during the test week. The 1.30 p.m. scores, however, are higher in all but two subjects on the benzedrine day than on the synhexyl days.

There was also an increased number of errors made by most subjects on the synhexyl days. Although not statistically significant, these results suggest that such effect as synhexyl has on intellectual activity impairs rather than improves it. It is interesting to note that Case 3, the one patient reporting general clinical improvement, nevertheless showed a falling off of work output at 1.30 p.m.

In Table II, practice effects overshadowed any statistically significant effects from other causes. The ratio of forward- to backward-written words and figures decreased steadily throughout the week. Under benzedrine the total number of words written, forwards and backwards, tended to be larger than under synhexyl. The trend in most subjects was for the ratio to rise with synhexyl, suggesting an increase in perseveration, or disposition rigidity as Cattell calls it. This trend was seen clearly only in the scores for the five-letter word, where practice is clearly least important, and Table II gives the values for this part of the test. This is of interest in that the clinical type Cattell describes as associated with high perseveration corresponds more closely to the synhexyl picture than does his low-perseveration type.

The defective will-power factor, as suggested by the persistence tests, would also tend to increase perseveration.

Table III gives the combined totals of figures and numbers recalled. The total remembered at the 1.30 p.m. tests is lower than either the 9 a.m. or 3.30 p.m. with both drugs, though the fall is greater with synhexyl than benzedrine. Again it is to be noted that the patient reporting improvement (3) did not do so well with synhexyl as with benzedrine.

Table IV gives the total time taken to tap out the six consecutive five-second periods. The overall picture shows no consistent changes, though the smaller dose of synhexyl tended to produce a longer time than the larger dose. It is interesting that Case 8, the most bizarre and psychotic at the time of testing, though her general personality was not the most unstable, gave consistent readings well below the true time and out of the range of the readings of the others. Case 6, who reported the clearest alteration of time perception, showed no significant change in this test. These negative results confirm Morrow's results in the New York report (1944) obtained by a slightly different technique.

In Table V the creative range of the block was not large enough to make any difference discernible in the quality of the designs produced. The mental set adopted by the subjects to the blocks remained relatively constant throughout the week and depended largely on what they felt to constitute a " different " design. More than one subject adopted the technique of making a basic pattern from most of the blocks and moving one block around it to make " new " designs. Others took " different " seriously and began from scratch on each new design. Interesting as these observations were from the point of view of personality differences, they told nothing of the action of the drug. However, the idea of the relatively free situation would seem to have possibilities.

The leg-raising tests (Table VI) showed the most unequivocal results, all subjects showing a fall in the time they held their legs up on synhexyl. With

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benzedrine a less marked rise in time was noticed. Several factors appear to be at work in producing these results. The demeanour of the patients suggested that the desire to please the doctor by doing well was an important factor in the length of time they held their legs up. Therefore when made worse with the synhexyl they expressed their thinly-veiled hostility by not trying so hard. Their general sleepiness and withdrawal of interest were other factors. In contrast, the breath-holding time (Table VII) showed little change throughout, presumably because imperative physiological needs allow such a short time for these psychological factors to operate.

Clinical Picture Produced by Synhexyl

The clinical picture produced by synhexyl may now be summarized as showing :

(1) an impairment of motor co-ordination and a lowering of psychomotor activity ;
(2) an increase in affective experiences and their physiological concomitants ;
(3) a withdrawal of interest from reality to fantasy ;
(4) a blunting of the finer intellectual processes ;
(5) a lowering of the will-power and concentration ;
(6) an impairment of the processes of perception ;
(7) clouding of consciousness.

It may be objected that these are all symptoms of an overdose, above therapeutic levels, but on the first group doses of 10 and 20 mg. were given with effects differing only in being less intense or negligible ; they were in no way qualitatively different. There is no evidence of a phase of improved performance before deterioration set in, as there is in some people after small doses of alcohol (Kürz and Kraepelin, 1901). A more serious objection to these findings as representative of the general effect of synhexyl is that subjects, predominantly depressed, tend to exaggerate unpleasant symptoms and minimize the more pleasant, but there is no evidence that the depressive state in itself is liable to make the action of a drug totally different. Kant (1930) gave hashish to a number of manic-depressives and schizophrenics on recovery from the acute phase of their illness and found that the former reacted by depression and increased or decreased psychomotor activity, whereas the latter were euphoric and often showed catatonic symptoms. The difference between the results of the present study and those reported by Stockings (1947) is more difficult to understand, but it is probable that the two groups of patients differed somewhat. Stockings' patients reported undesirable side effects, as ours did, especially in the earlier stages of drug effect, and in the later stages showed euphoria. Several of our patients were certainly euphoric at the height of the drug action, but in the fatuous, insightless, confused manner of the slightly " tipsy."

There would appear to be a difference of opinion about the nature of euphoria and its therapeutic usefulness. Even the word " euphoria " appears to be undergoing a change of meaning, from its original sense of normal bodily well-being to a sense of abnormal well-being such as characteristically occurs in alcoholic intoxication.

Comparison of Synhexyl and Benzedrine Effects

It is unnecessary even to summarize the well-known effects of benzedrine which are described in numerous papers. The effects of synhexyl and benzedrine in this group of subjects were in marked contrast, not only in that most subjects were made worse by the former and improved by the latter, but also, as has been mentioned previously, in that the one subject improved by synhexyl was made worse by benzedrine. It is difficult to think of any adequate explanation of this phenomenon, and any speculations along the lines of a sympathetic-parasympathetic imbalance are unfortunately unsupported by any evidence that synhexyl has any parasympathetic activity. Neither is anything known about the metabolism of synhexyl which would link it with the biochemical effects observed by Mann and Quastel (1940). Loewe (1944) reports that in animals benzedrine has a marked potentiating effect on the ataxia produced by marihuana ; but, as in this series the drugs were administered on different days, there are no data relevant to his observations.

From the therapeutic point of view this small series clearly shows the superiority of benzedrine over synhexyl in alleviating depressive states. The psychological tests also show that synhexyl has a more deleterious effect on performance and efficiency than benzedrine. The most marked contrast is seen in the persistence tests, but small effects are noticeable in the adding, concentration, and perseveration tests. The undesirable side effects of synhexyl seem a high price to pay for the doubtful therapeutic value of euphoria and an easing of obsessional thought pressure.

Mode of Action of Marihuana Derivatives and Homologues on the Central Nervous System

A large number of marihuana derivatives and their homologues have been studied, synhexyl being chosen as the most active of these. The tests employed in their assay are all biological, and only

one—the amount required to produce ataxia in dogs—is at all reliable. Other methods of assay—based for example on a synergistic hypnotic action in the mouse, or the production of corneal areflexia in the rabbit—have been shown to be due to compounds in marihuana not closely related to synhexyl. During assays in dogs, convulsant spasms are reported to be of frequent occurrence, and at least one derivative has a marked tendency to produce epileptic fits. Detailed studies of the relation between chemical structure and pharmacological activity are summarized by Loewe in the New York report (1944) and do not concern us here. Further reviews have been given by Todd (1945) and Adams (1942). The mechanism of action of Marihuana has been experimentally investigated by Joel (1925). His aim was a limited one, as the investigation was part of a series on the vestibular reactions. Joel reports that in intact cats marihuana produces a catatonic picture with swaying, decrease in motility, and cataleptic perseverance. A similar picture was found by Loewe (1945). In decorticate cats swaying is the only sign, while in decerebrate animals there are none. Wikler and Lloyd (1945) using bipolar occipital leads only, investigated electro-encephalograms taken after patients had smoked two or three marihuana cigarettes. There was no significant change in alpha frequency, and in only some of the patients was there a slight decrease in alpha time. Muscle artefacts obscured any cortical fast frequencies. In cats light mixtures of marihuana smoke and air caused the disappearance of from 6 to 9 c/sec. activity, but more concentrated smoke caused a slowing of cortical activity. The New York report (1944) mentions that electro-encephalograms taken by Strauss showed an increase in alpha activity. The only conclusion that can be drawn from this is that the higher physiological functions—those mediated by cortex and thalamus in their normal inter-relationship—are the most easily disturbed by marihuana. Most observers are agreed that it is a drug whose central action far outweighs any peripheral effects (for example, Walton, 1938).

According to the New York report the general metabolic changes produced by marihuana are few, Beringer and others (1932) describe more marked changes which suggest that his subjects were in a rather toxic and dehydrated condition. All the changes described, however, throw no definite light on the effect of the drug on the central nervous system.

From the study here reported one may say that synhexyl acts predominantly on the "higher" functions. It appears to impair the activity of most areas of the cortex, although these functions which are commonly localized in the frontal lobe appear to be most affected. In fact the only symptoms which are in contrast to the familiar "frontal-lobe syndrome" are the increased introversion of interest and the clouding of consciousness. The latter may well be secondary to the disturbances in function of so many different spheres of cerebral activity.

Summary

The effects of synhexyl, a homologue of one of the active principles of marihuana, have been investigated in a group of patients with predominantly depressive characteristics. The symptoms produced were those of general impairment of cerebral function and mild clouding of consciousness. No evidence that the drug is valuable as a treatment for depression was obtained. The symptoms produced were in contrast to those of benzedrine in the same group of subjects. These findings are discussed in relation to the mechanism of action of the drug.

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REFERENCES

Adams, R. (1942). *Bull. N. Y. Acad. Med.*, **18**, 705.
Beringer, K., von Baeyer, W., and Marx, H. (1932). *Nervenarzt*, **5**, 337.
Cattell, R. B. (1946). *J. Pers*, **14**, 229, 239.
Douthwaite, A. H. (1947). *Brit. med. J.*, **2**, 43.
Eysenck, H. J. (1947). "Dimensions of Personality." Kegan Paul. London.
Joël, E. (1925). *Pflug. Arch. ges. Physiol.*, **209** 526.
Kant, F. (1930). *Arch. Psychiatrie*, **91**, 694.
Kürz, E., and Kraepelin, E. (1901). *Psychologische Arbeiten*, **3**, 417.
Loewe, S. (1944). In "The Marihuana Problem in the City of New York." New York Mayor's Committee. Jacques Cattell Press.
——. (1945). *Fed. Proc.*, **4**, 127.
Mann, P. J. G., and Quastel, J. H. (1940). *Biochem. J.*, **34**, 414.
Mayer-Gross, W., and Guttmann, E. (1936). *J. Ment. Sci.*, **82**, 222.
Morrow, R. (1944). In "The Marihuana Problem in the City of New York."
Stockings, G. T. (1947). *Brit. med. J.*, **1**, 918.
Todd, A. R. (1945). *Experientia*, **2**, 55.
Walton, R. P. (1938). "Marihuana, America's New Drug Problem." J. B. Lippincott and Co. Philadelphia.
Wikler, A., and Lloyd, B. J., Jr. (1945). *Fed. Proc.*, **4**, 141.

CYSTIC PITUITARY ADENOMATA

BY

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Review of the Literature

References in the literature to cystic adenomata of the pituitary gland are by no means numerous. In a survey we have found surprisingly little discussion of this type of tumour, though it occurs with sufficient frequency to make its study of some practical importance from the point of view of both prognosis and treatment.

In Cushing's (1912) pioneer work on the surgery of the pituitary gland only one of his early operative series of twenty pituitary "strumas" is noted as cystic; one other case, the famous giant, Turner (not operated on), was found at necropsy to have his pituitary adenoma almost entirely replaced by a large cyst. The small proportion of cysts in this early group of cases is curious, differing as it does so greatly from that found in other more recent series. Cushing was keenly alive to the very satisfactory decompression which should result from the evacuation of such cysts by the transphenoidal operation, and it seems unlikely that he failed to observe the escape of fluid when he incised the capsule of the gland from below.

When we pass to the modern era, with the operative approach predominantly transfrontal, we find a discussion of the cystic adenomata by Grant (1939), who emphasizes that these tumours have distinctive features from the standpoint of both prognosis and treatment, when compared with the solid growths. By far the most important and detailed report on the subject is Henderson's (1939) paper on the pituitary adenomata in Cushing's clinic, which deals with all the operative material from 1913 till 1932. He reported 338 cases of pituitary tumours, among which there were 49 with cyst formation.

It seems to be generally agreed that the cystic lesions show certain differences in behaviour when compared with the solid tumours. In particular it is stated that operations on the cystic cases result in a greater and more rapid improvement in the visual fields; that postoperative recurrence of visual field defects occurs more frequently; and that the cysts are more radio-resistant. Two varieties of cystic fluid are described; one clear, yellow in colour, the other dark reddish or brown and opaque. The proportion of cystic to solid tumours has been variously estimated at from 17 to 43 per cent., 17 per cent. is Henderson's figure for Cushing's series; Grant in a review of the literature found 25 per cent. to be cystic, but his own personal series contained 43 per cent., a figure which, as we shall see later, is probably not comparable with the others. The occurrence of an acute hæmorrhagic cyst has been described by Cushing (1926) and Sosman (1939). The latter reports a patient who after a course of *x*-ray treatment for postoperative recurrence of a pituitary tumour went into coma in a few hours; a hæmorrhagic cyst was found at operation and was evacuated with recovery.* The occurrence of this considerable proportion of cystic adenomata has practical importance if, as most writers believe, they are more radio-resistant than the solid growths, for this would provide an argument for the treatment of the pituitary adenomata by operation, rather than by radiation.

What should be our criterion of cyst formation when we expose the lesion at operation? Grant found 43 per cent. of his cases to be cystic, but he included tumours in which, on incision of the

* Since this paper was written we have encountered a case of acute hæmorrhage into a pituitary adenoma. A woman aged sixty-two had noticed for some months that the vision in her right eye was failing. Two evenings before admission she complained of headache and vomited several times that night. Next morning she was completely blind in both eyes. When examined next day the loss of vision was found to persist, with dilated fixed pupils and palsy of all the oculomotor nerves of both eyes except the left sixth. There was a typically ballooned sella in the radiographs. At operation on the day after admission a large chromophobe pituitary adenoma, with its dural capsule intact, was seen. It contained a large amount of blood-clot, some recent and some which, from its brown colour, its toughness, and its adherence to the tumour capsule, was thought to be of at least of some weeks' standing. After operation the patient remained in a stuporose state, from which she could be roused to carry out simple commands and to take nourishment, until her death three weeks later. There was no recovery of vision and the ocular palsies persisted. Towards the end the optic discs were becoming pale.

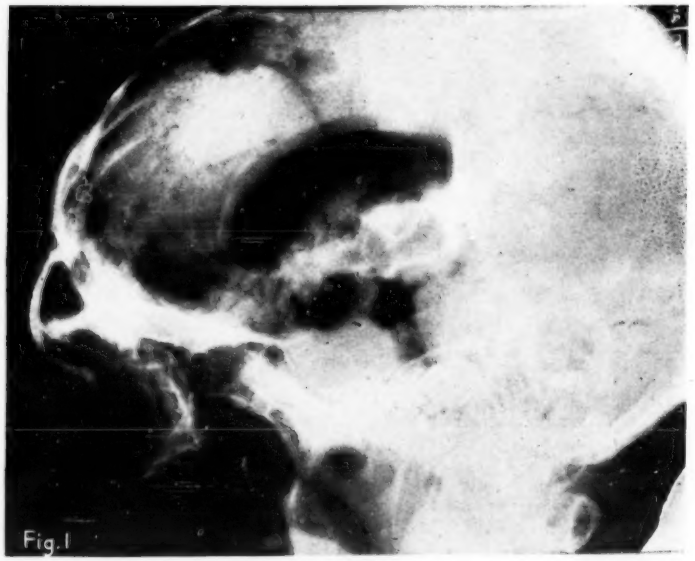

FIG. 1.—Lateral encephalogram, showing the hydrocephalus, the wide cisterna chiasmatis, and the recurrent pituitary adenoma.

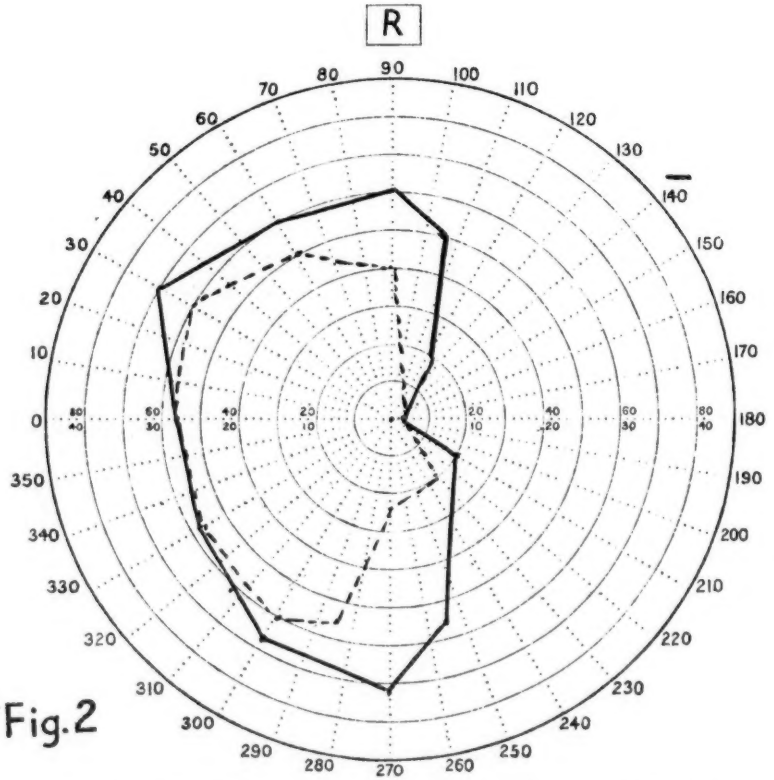

FIG. 2.—Pre-operative visual-field chart of the right eye, examined on June 14, 1937. At this time the left eye was almost blind. (. . . . 3/330 mm. white ; ——15/330 mm. white.)

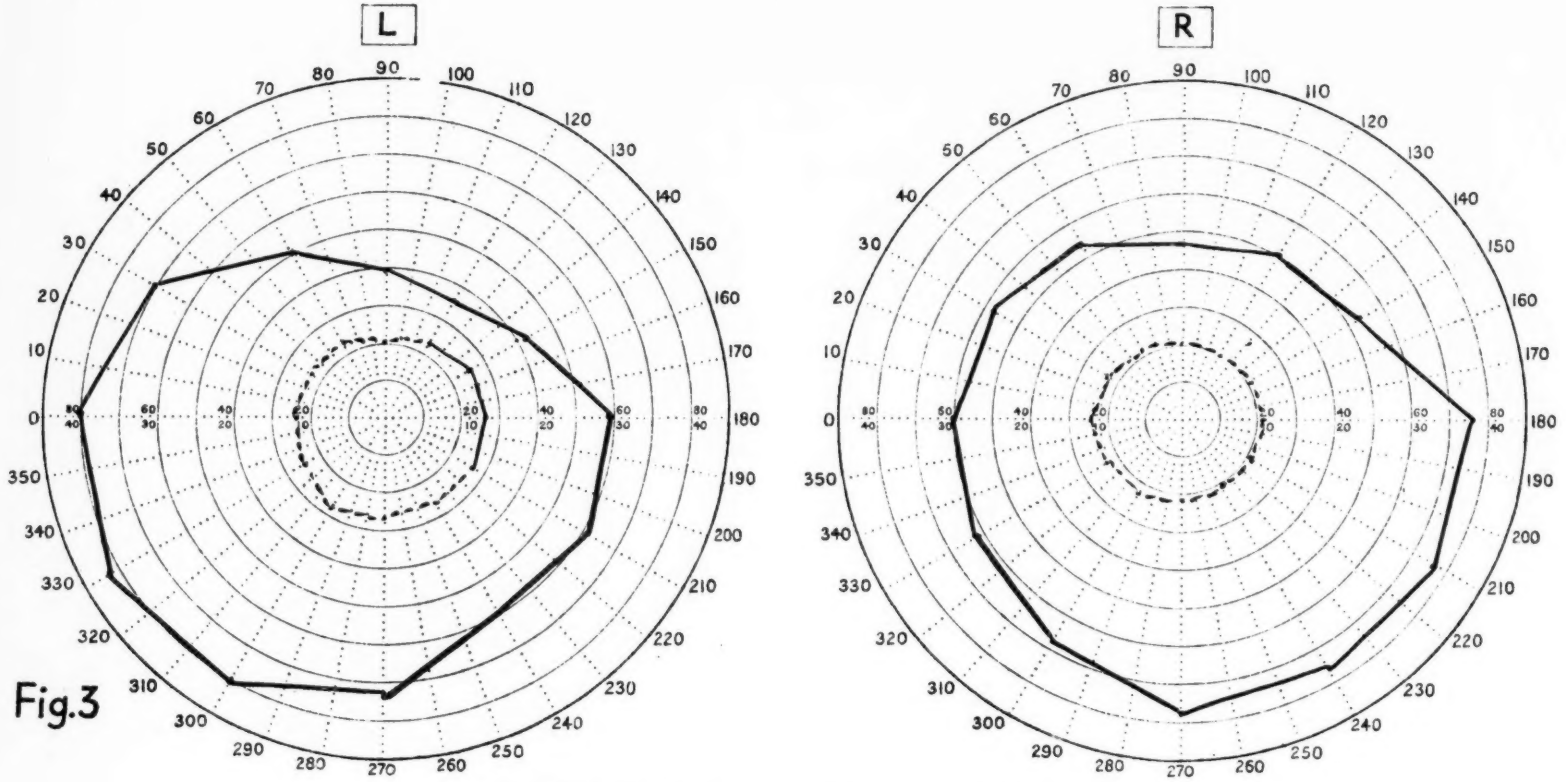

FIG. 3.—Post-operative visual field charts taken on Aug. 21, 1938 (the patient was operated on, on June 16, 1937). Vision at this examination was 6/6 in each eye. (. . . . 3/1,000 mm. white ; ——3/330 mm. white.)

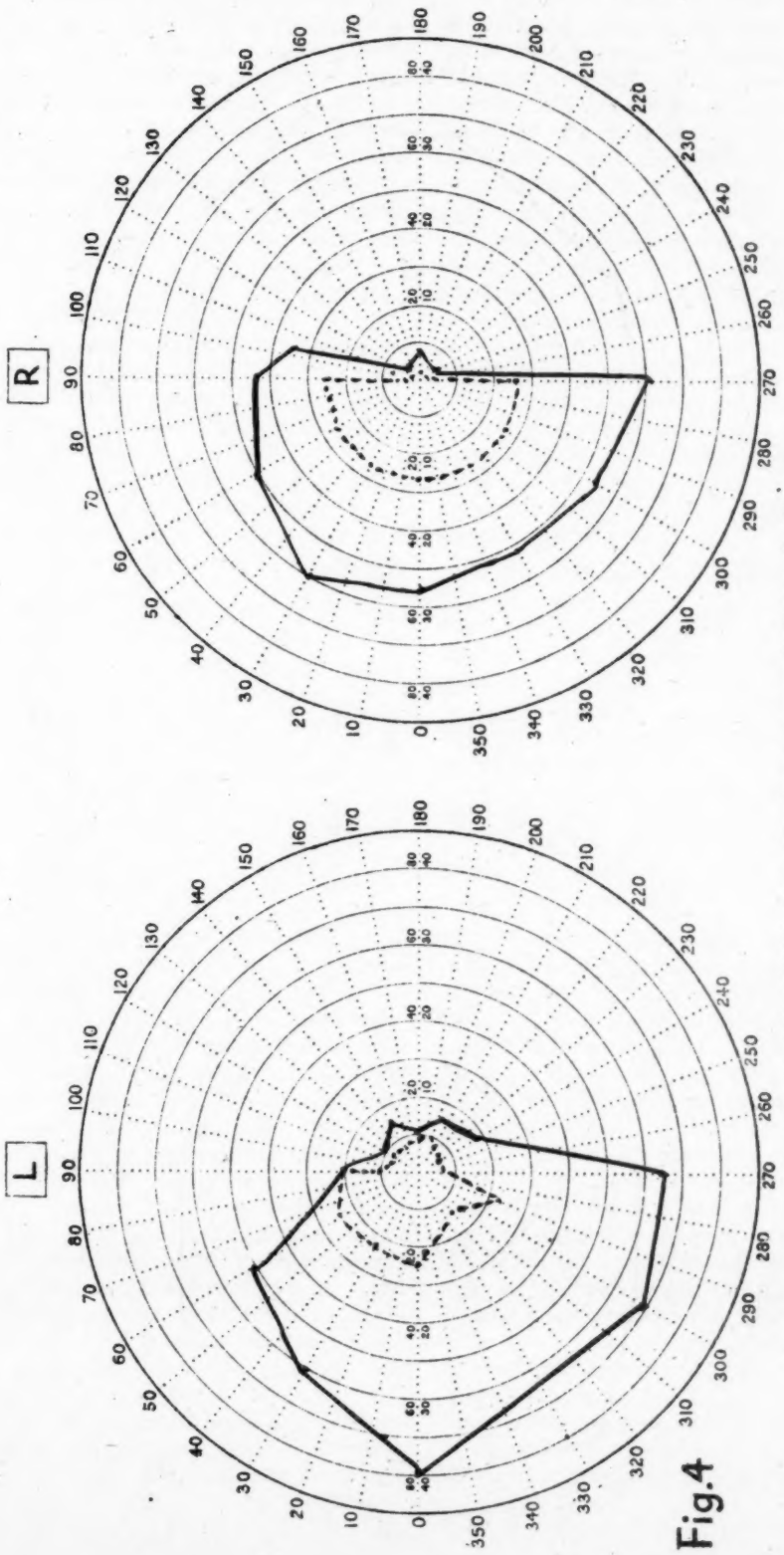

FIG. 4.—Visual field charts showing post-operative relapse on Oct. 8, 1939. Vision was 3/4 in each eye. (. . . . 3/1,000 mm. white; ——3/330 mm. white.)

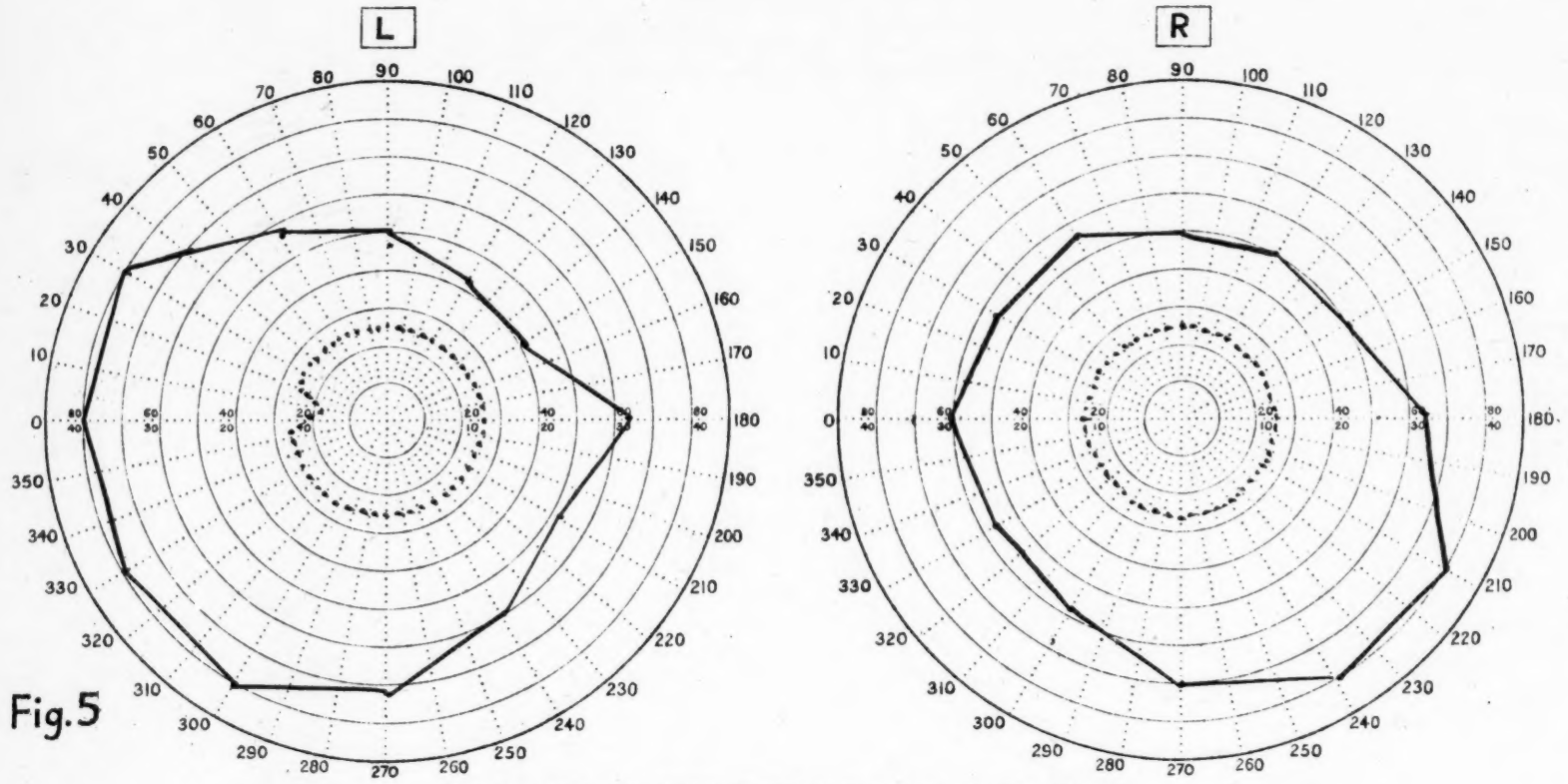

FIG. 5.—Deep *x*-ray treatment was begun on Oct. 17, 1939, and the above are visual field charts taken a year later, on Oct. 13, 1940. (. . . . 3/1,000 mm. white ; ——3/330 mm. white.)

capsule, the contents flowed out " with prompt or slow collapse of the mass." This implies a very wide definition of the term cyst, for it must include a number of tumours with very soft contents, which protrude when the capsule is incised and which, following Jefferson (1940), we would rather class as diffluent. We reserve the term cystic for those tumours from which the operator can aspirate an appreciable amount of fluid through a spinal needle. Using this criterion a fair proportion at least of the contents must be fluid.

The Present Series

If we define our cystic tumours in this fashion we find that, of forty-nine pituitary adenomata operated on, ten were cystic (20 per cent.). This proportion is not far removed from the 17 per cent. of Henderson's series.

Aspiration of the cystic fluid allows us to measure its quantity. Unfortunately we have no note of this in three of the cases, but in the remaining seven it was found to vary between 4 and 17 c.cm., with an average of about 10 c.cm.

Our experiences confirm that two distinct types of cyst content occur. In the first group the fluid is clear and yellow. The depth of the yellow coloration varies, much as it does in the cyst fluid of astrocytomas ; in one case it was so pale as to be almost colourless, while in others the colour was deep golden orange. One example clotted spontaneously when allowed to stand in a test-tube, and it is possible that other specimens might have shown this property if they had been examined after standing. This spontaneous clotting is well known to occur in the fluid from cystic astrocytomas and hæmangioblastomas, and as we shall see later it may be produced by a similar mechanism. There were four cases with clear yellow fluid in the series. In the second group the fluid was dark and had sometimes the appearance of old blood, but in three tumours its characters were noted as typical of the contents of a Rathke's pouch cyst, brownish " motor-oil " fluid shimmering with cholesterol crystals. At one time we were under the impression that this type of fluid was pathognomonic of Rathke's cyst, and we feel it is important to appreciate that such brownish, cholesterol-containing cyst contents may occur in chromophobe pituitary adenomata. The operative and postoperative treatment of these two lesions is by no means identical, and the lesson to be drawn is that there should be a biopsy report in all such cases before operative closure.

With two exceptions, these cystic tumours were indistinguishable in their gross appearances from the solid ones, and were appreciated as cystic only when aspirated. One unusual finding was in the case of a girl with one eye blind and an advanced field defect in the other, whose clinical aspect was that of acromegaly with terminal hypopituitarism. The cyst wall was so densely calcified as to show up clearly in the radiographs ; so dense was the calcification that bone rongeurs had to be employed to cut through the capsule after 13 c.cm. of thick, dark brown fluid had been aspirated. The other case was a chromophobe adenoma re-operated on for signs of recurrence two years after the primary operation. The wall of the large cyst was so thin as to appear bluish in colour ; its contents were dark brown fluid.

There was one fatal case in the series. At operation a large cyst had yielded 16 c.cm. of brown fluid. Necropsy showed the lesion to extend backwards across the remains of the dorsum sellæ under the hypothalamus and to be distended with recent blood-clot ; there had been a postoperative hæmorrhage into the cyst.

Biopsy Findings.—Biopsy specimens of nine of the ten cases showed histological appearances indistinguishable from those of the ordinary solid tumours ; eight were chromophobe adenomas, one acidophil. The only unusual picture was found in the fatal case just described, in which there were large thyroid-like vesicles, such as are seen in the pars intermedia of the normal gland. It is interesting that Cushing described such a tumour in his first monograph (1912). He pointed out the histological similarity to thyroid tissue, and suggested that some suprasellar growths may originate in the pars intermedia.

Cystic and Solid Tumours.—Is there any evidence in our series of cases that, as a review of the literature suggests, the adenomas with cystic contents are more liable to recur than the solid ones? Nine cystic and thirty-nine solid tumours survived operation. Of these it is known that four of the former and six of the latter had a recurrence of visual field defects. At first sight this seems to confirm the greater tendency to recurrence of the cystic adenomata, but the two series are not comparable in that, while the treatment of the solid growths was, from the first, operation followed by *x* radiation, it was not until 1939, when the case reported below showed signs of recurrence, that radiation was used in the postoperative treatment of the cystic cases. We have thus no real evidence of the greater proneness to recurrence of the cystic growths.

Our experience is that recovery of vision and expansion of fields tend to be more rapid and more complete in the cystic cases. Failure of vision and visual-field defects in cases of tumour in the region

of the chiasma are the result of changes in the visual pathways which may be either reversible or irreversible, and the extent of the postoperative recovery of vision must depend upon how complete is the relief of pressure on chiasma and optic nerves and upon the proportion of damage which is irreversible. It seems reasonable to assume that the amount of such damage must vary with the duration of the pressure on the chiasma and its blood vessels. In the slow-growing craniopharyngiomas the extent of the postoperative expansion of the visual fields is often very disappointing. The cystic adenomata, on the other hand, in which the operative relief of chiasmal pressure is complete and in which failure of vision is often of short duration, are among the most satisfactory of all chiasmal lesions ; they are above all others those in which, as Cushing pointed out long ago, the neurosurgeon shares with the ophthalmologist the supreme satisfaction of restoring vision. It seems reasonable to assume that this rapid and sometimes complete recovery of sight may be correlated with the rapid development of the cyst and a chiasmal pressure of short duration.

The Cyst Content.—Why are so many of these adenomata cystic, and why are the cyst contents sometimes a clear yellow fluid which may coagulate on standing and sometimes dark and opaque, like altered blood ? The clear yellow fluid is similar to that found in the cystic astrocytomata and hæmangioblastomata, and it is suggested that a similar mechanism may be responsible for its production. The thin-walled tumour vessels may be unduly permeable to the blood plasma, allowing the passage not merely of albumen and globulin but, as in the case in which spontaneous clotting occurred, of fibrinogen as well. Where, on the other hand, the fluid is dark and opaque, we may imagine the vessel walls to have ruptured, with resulting hæmorrhage. Another factor may be a disturbance of the tumour circulation resulting from its enclosure in a rather unyielding fibrous and bony capsule ; a state of affairs resembling that produced by a space-occupying intracranial lesion, in which a rise in venous pressure is an early feature. This high intracapsular pressure is often demonstrated by the extrusion, like tooth-paste from a tube, of the soft tumour contents when the capsule is incised, and a rise in venous pressure might be expected to encourage the escape of some or all of the elements of blood through the vessel walls.

The following case report is of interest as exemplifying the rapid and complete restoration of vision after operation, the tendency to relapse, and the danger of an overdose of *x* radiation.

Case Report

A man aged 51 was seen first in 1937, when he presented the signs and symptoms of a chromophobe pituitary adenoma, with a temporal field defect of the right eye, and a blind left eye (Fig. 2.). At operation a cystic adenoma was found containing 17 c.cm. of dark fluid, obviously old blood. He had no postoperative radiation at this time. After operation there was a rapid expansion of both fields of vision, which four months later were both full, with 6/6 vision in each eye (Fig. 3). Two years after operation there was a relapse, and it is of interest that the visual fields now showed a right homonymous hemianopia of incongruous type, indicating pressure on the left optic tract (Fig. 4). Deep *x*-ray therapy was given, and there was once more a great expansion of the fields (Fig. 5). It seemed likely that there was a nodule of solid tumour, extending from the left lateral wall of the cyst ; for it is difficult to imagine a cystic midline tumour sparing the chiasma so completely.

Another relapse occurred in 1943 ; operation was advised but was refused, and another course of *x* radiation was given. There was very little improvement in the visual fields on this occasion, and thereafter the patient's general condition deteriorated. He was readmitted in 1945, when he was found to be bedridden and doubly incontinent, with signs of gross disturbance of hypothalamic function, stupor, and mental confusion. Cisternal encephalography (Fig. 1) gave an interesting picture for the pituitary tumour was seen to be outlined by gas in a chiasmal cistern which, with the interpeduncular cistern, was grossly dilated, suggesting atrophy of the hypothalamus. Death occurred at home a few months later ; there was no necropsy.

It is difficult to avoid the conclusion that this terminal hypothalamic atrophy was the result of an overdose of *x* rays ; the total dosage, calculated as delivered to the pituitary area, was 9,450 r.

Summary

Operative and postoperative experiences with ten cases of cyst formation in a group of forty-nine pituitary adenomata are reported. Cyst formation was found to occur in 20 per cent. of the series, and the cyst contents were found to be either a clear yellow, or a dark, brownish, opaque fluid. In three cysts in the latter group the fluid contained cholesterol crystals and was identical in naked-eye appearances with that found in cysts of Rathke's pouch. The importance of this finding in the differential diagnosis and treatment is indicated. Histologically the tumours, with one exception, were indistinguishable from other pituitary adenomata ; one was acidophil, the remainder chromophobe. The exceptional case showed large thyroid-like vesicles, suggesting an origin from the pars intermedia. Recovery of vision and expansion of fields were thought to be more rapid and complete in the cystic tumours than in the solid growths. The history is given of a patient in whom, after

operation followed by great improvement in vision, two recurrences were treated by *x* radiation, with subsequent signs and symptoms of fatal hypothalamic atrophy.

We wish to express our grateful thanks to Dr. Margaret Leslie, Pathologist, Killearn Hospital, who has examined all the biopsy material and has provided the photographic reproduction of the encephalogram.

REFERENCES

Cushing, H. W. (1912). "The Pituitary Body and its Disorders." J. B. Lippincott Co., Philadelphia. p. 304.
——(1926). "Studies in Introcranial Physiology and Surgery." Oxford University Press, London. p. 56.
Grant, F. C. (1939). *J. Amer. med. Ass.*, **113**, 1279.
Henderson, W. R. (1939). *Brit. J. Surg.*, **26**, 811.
Jefferson, G. (1940). *Proc. roy. Soc. Med.*, **33**, 433.
Sosman, M. C. (1939). *J. Amer. med. Ass.*, **113**, 1282.

CASE REPORT: ABNORMAL INNERVATION OF THE SPHINCTER PUPILLÆ AND CILIARY MUSCLE FOLLOWING THIRD-NERVE REGENERATION

BY

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Bender and Fulton (1939) showed that in monkeys, following regeneration of the sectioned third cranial nerve, a mass innervation of the muscles supplied by the third nerve develops. This resulted in limitation of upward and downward movement of the eye owing to synkinesis of the antagonist muscle. Recovery of inward movement was good, but was associated with pupillary contraction. Ford, Walsh, and King (1941), and Bender (1945), pointed out that after regeneration of the oculo-motor nerve in man pupillary constriction on convergence may be one of several synkineses observed, and, as the pupil is often inactive to light a "pseudo-Argyll-Robertson" pupil phenomenon may appear. It seems that indiscriminate regeneration through the scar on the injured nerve leads to this phenomenon, and Bender reported cases in which the pupil reacted on contraction of any one or all of the formerly paralytic muscles. He also described a case in which there was synkinetic contraction of both the ciliary muscle and the sphincter pupillæ in association with eye movement. Schretzenmayr (1947) studied similar synkinetic movements of the upper eyelid.

In the following example of this phenomenon both the sphincter pupillæ and the ciliary muscle contract when the eyeball is turned inwards.

Case Report

On July 11, 1944, a bombardier, aged 29, had a severe motor-cycle accident which caused fracture of the left parietal bone and base of the skull. There was bleeding from the left ear. The duration of retrograde amnesia was about one minute, and of post-traumatic amnesia ten days.

His physical recovery was satisfactory except for ocular palsies affecting the left eye. He was reported during convalescence to have left ptosis; the left pupil was dilated and inactive; all movements of the left eyeball were lost except for slight upward and downward movement. There was analgesia of the left upper lip, and slight deafness of the left ear.

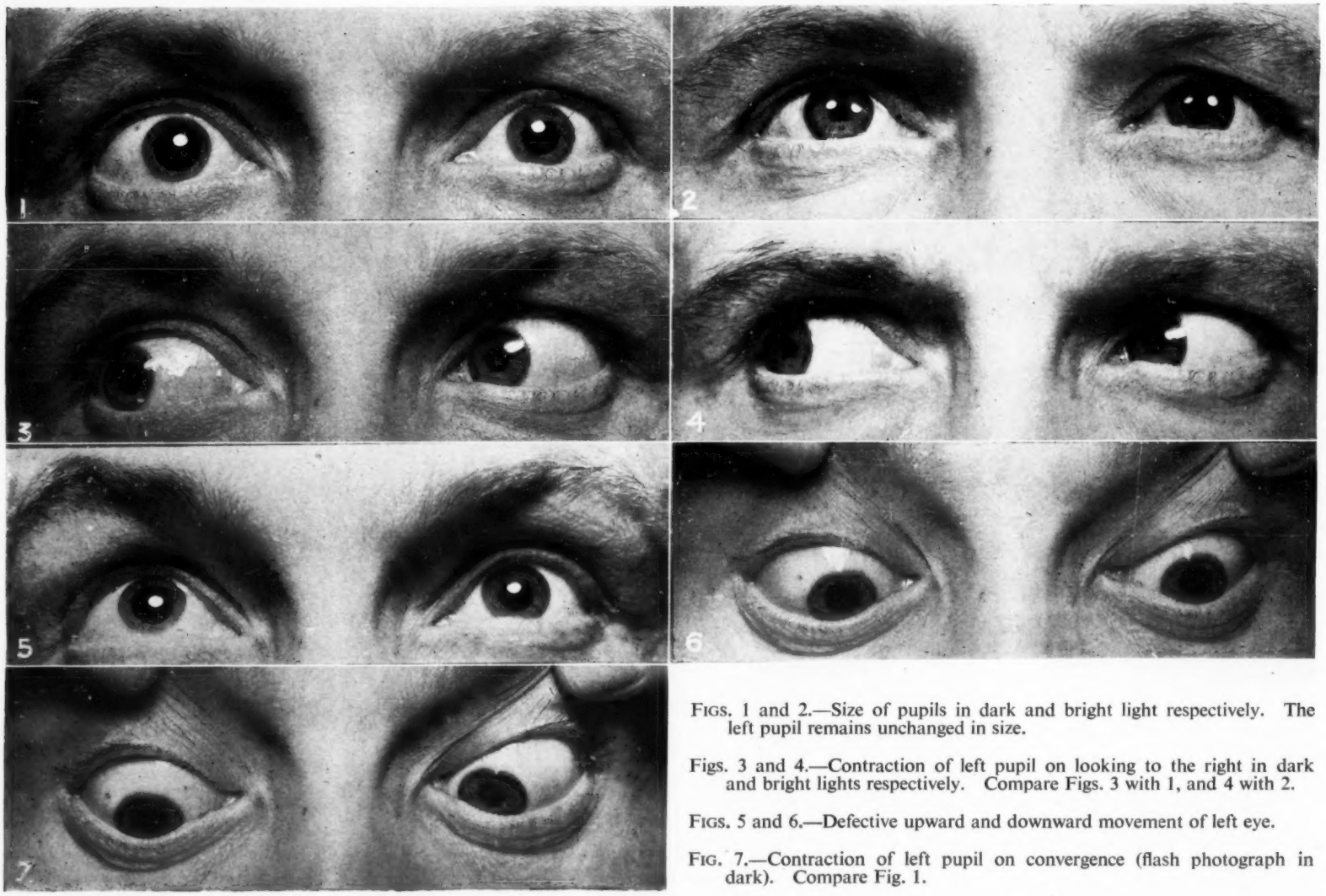
He was invalided from the service in December, 1944, and returned to work as a mechanic and driver in January, 1945. Later he left this work as looking upward made him feel giddy, and for the past year has been working as a handyman. He complains now (May, 1948) of deafness in the left ear, paræsthesiæ over the left cheek, and difficulty in reading. The visual difficulty appeared to be due to paralysis of accommodation of the left eye while the right eye "had never been strong." Examination of the eyes revealed some interesting abnormalities.

Figs. 1 and 2 illustrate respectively the size of the pupils in the dark and when exposed to a bright light. The absence of light reaction in the left pupil is quite evident. Ocular movements to the left appeared to be full in both eyes: upward and downward movement of the left eye were defective (Figs. 5 and 6). *On looking to the right the movement of the left eye was good, but was associated with well-marked contraction of the pupil.* This is seen in Figs. 3 and 4, Fig. 3 being in the dark and Fig. 4 in bright light (compare Figs. 1 and 2 respectively). A similar contraction of the left pupil occurred on convergence, as is seen in Fig. 7 (photograph by flash in the dark).

Further, not only was the sphincter pupillæ made to contract by deviating the left eye to the right, *but also the ciliary muscle was thrown into activity.* Visual acuity in the left eye was full at six metres (6/6), but owing to paralysis of accommodation the near vision of the left eye was reduced to J 12. However, when the Jæger type was held to the right so that the left eye turned inwards, the near vision improved to J 1, clearly indicating that this inward movement of the eye caused contraction of the ciliary muscle.

Ophthalmological Examination.—Ophthalmological examination revealed the following:

Right Eye.—This eye showed no abnormality apart from a refractive error; he had never used correction for this eye. Visual acuity (unaided) was Snellen 6/60; corrected $-3{\cdot}5/+5{\cdot}0$, 110° it was Snellen 6/18, Jæger 4.



FIGS. 1 and 2.—Size of pupils in dark and bright light respectively. The left pupil remains unchanged in size.

Figs. 3 and 4.—Contraction of left pupil on looking to the right in dark and bright lights respectively. Compare Figs. 3 with 1, and 4 with 2.

FIGS. 5 and 6.—Defective upward and downward movement of left eye.

FIG. 7.—Contraction of left pupil on convergence (flash photograph in dark). Compare Fig. 1.

Left Eye.—There was no ptosis ; the conjunctiva, cornea, anterior chamber, media, and fundi were normal. The left pupil was larger than the right, and showed no reaction to direct or consensual light. There was a sluggish contraction on convergence. The left pupil contracted briskly on turning the eye 30° to the right (inwards), and dilated on turning the eye to the left.

Visual acuity looking straight ahead (unaided) was Snellen 6/5, Jæger, less than 12. Retinoscopy : $-\left|\begin{matrix}+1{\cdot}0\\ \text{——}\\ +1\,0\end{matrix}\right.$.

Visual acuity on looking 30° *to the right* (unaided) was Snellen 6/24, Jæger 1. Retinoscopy : $-\left|\begin{matrix}-1{\cdot}0\\ \text{——}\\ -1{\cdot}0\end{matrix}\right.$.

Extrinsic Ocular Movements.—There was limitation of the upward and downward movement of the left eye. The Hess diplopia chart suggested paresis of the left inferior oblique, inferior rectus, superior oblique, and superior rectus muscles.

Intrinsic Ocular Movements.—Accommodation as measured by the Livingstone Gauge was as follows :

Looking straight ahead ..	34 cm.
Looking 20° (approx.) to the right (inwards)	22 cm.
Looking 30° (approx.) to the right (inwards)	14 cm.
Looking 20° (approx.) to the left (outwards)	49 cm.

Discussion

These findings illustrate clearly the abnormal regeneration of the oculo-motor nerve with mass innervation of the muscles supplied. Previous attempts to give the patient reading vision had been directed towards correcting the refractive error in his " lazy " right eye. A plus lens provided for the left eye enabled him to read with comfort.

References

Bender, M. B., and Fulton, J. F. (1939). *J. Neurol. Psychiat.*, **2,** 285.
——(1945). *Arch. Neurol. Psychiat., Chicago,* **53,** 418.
Ford, F. R., Walsh, F. B., and King, A. (1941). *Bull. Johns Hopk. Hosp.*, **68,** 309.
Schretzenmayr, V. (1947). *Deut. zeit. Nervenh.*, **158,** 43.

A CASE OF CEREBRAL AMOEBIC ABSCESS TREATED BY MODERN CHEMOTHERAPY

BY

E. A. TURNER

(RECEIVED JUNE 9, 1948)

The following case history is presented for two reasons. A case of cerebral amœbic abscess is comparatively rare in itself: Stein and Kazan in 1942 described the sixtieth case reported in the literature at that time. In only fifteen of these sixty were amœbæ actually seen in the contents of the abscesses. Secondly, this case presents unusual and fresh features in that it was treated by penicillin in addition to surgery and sulphonamides, and that the duration of the illness extended for four and a half months, far beyond the usual maximum duration of ten to fifteen days. Had anti-amœbic treatment been given at the outset of treatment for the cerebral abscess even the ultimate fatal result might have been different. It is open to speculation whether cerebral amœbic abscess may not sometimes be curable with modern chemotherapy. All the published cases to date have ended fatally.

Case Report

The patient, aged 20 years, had served in the Army for one year, nine weeks of which were spent in India. No details of service in any other country where amœbiasis is endemic are known. He was admitted to a Military Hospital in India on Feb. 6, 1946, with a two days' history of headache, pain behind the eyes, fever, and constipation. No abnormal signs were found on admission except for pyrexia. Three days later the headache became more severe, and two small bright red macules were noticed on the dorsum of the right hand. Similar macules appeared next day on the face, arms, chest, and abdomen, and were accompanied then by nuchal rigidity and a positive Kernig's sign. Next day, that is seven days after admission, the patient had a mild rigor and developed a dry cough and dyspnœa. This was followed by epistaxis, pain in the chest, and dullness and bronchial breathing at the bases of both lungs.

On admission the white blood cell count was 16,000 per c.mm. of blood (polymorphs 75 per cent., lymphocytes 19 per cent., monocytes 5 per cent., eosinophils 1 per cent.). The cerebrospinal fluid on Feb. 11 was clear, without increase of cells: protein was 55 mg. per 100 c.cm., globulin slightly increased, sugar and chlorides normal. The pressure was not measured. Blood culture was sterile. The urine was clear and contained no blood cells in the deposit.

On Feb. 14 the white blood cells numbered 24,000 per c.mm. of blood (polymorphs 85 per cent., lymphocytes 11 per cent., monocytes 4 per cent.). Intramuscular injections of sodium penicillin were begun, 20,000 units being given every three hours.

On Feb. 15 it was noticed that the patient was dysphasic. This disability was severe even on that day, as he could say only a few monosyllabic words in addition to "yes" and "no." He could understand simple commands but quickly perseverated. He had weakness of the right face and arm, and to a less extent of the right leg. The right plantar reflex was indefinite. He gradually became worse, without any dramatic change in the signs, until on Feb. 25 he was stuporose. A radiograph of the skull showed no abnormality. The chest at that time had radiological evidence of consolidation at the right base, with a raised right diaphragm. Papillœdema was noted. The cerebrospinal fluid pressure was 380 mm.

On Feb. 26 a left temporal incision and burr hole were made, and an abscess cavity located in the brain at a depth of 1 cm.; 8 c.cm. of pus was removed, and penicillin inserted. A course of general chemotherapy was given: penicillin 30,000 units three-hourly, and sulphamezathine 5 g. followed by 3 g. four-hourly.

By Feb. 27 he had deteriorated until the only word he could say was "yes." He had developed a bilateral sixth and a partial left third cranial nerve palsy. Bilateral burr holes were made, showing normal cortex. The right ventricle was tapped, the fluid being clear and colourless. The previous subdural operation site was re-explored and drained freely, with insertion of penicillin. Thereafter the patient improved somewhat, but did not lose completely any of the abnormal signs. The cerebrospinal fluid protein was 90 mg. per 100 c.cm., globulin increased, white cells 7 per c.mm., Wassermann reaction negative, Lange 1111000000.

On March 1 chains of streptococci were seen in a direct smear of the pus. No organisms, however, were grown on culture, either ærobically or anærobically. The failure to culture the organisms may have been due to the fact that no paraminobenzoic acid was available to inhibit the sulphonamides, which were presumably present in the pus from the course of chemotherapy which had been commenced three days previously.

During the next few weeks he alternately improved and relapsed. The first course of chemotherapy was stopped on March 18, by which date he had been given 5 million units of penicillin and 378 g. of sulphamezathine.

On March 25 the maculo-papular rash recurred, and that same afternoon his condition deteriorated again. The rash subsequently became vesicular. He was again given sulphamezathine and penicillin.

Ventriculography on March 27 showed a block between the two ventricles and a marked generalized shift to the right. Exploration of the left hemisphere yielded negative results until the needle finally entered a firm-walled abscess cavity flattened against the left side of the falx posteriorly : this was outlined by injection of thorotrast. The pus showed no organisms on direct smear, and was sterile on culture ; 100 c.cm. was removed on the first occasion, and 15 c.cm. two days later.

Next month nuchal rigidity became marked and pyrexia returned. On April 12 coarse tremor and involuntary twitching were noted in the muscles of the face and upper limbs. This was taken to be tetany. Sulphonamides and alkalis were therefore stopped, and calcium gluconate was given, but without benefit. In the light of subsequent events it seems that this muscular twitching was probably due to ventricular irritation, as it is commonly seen in cases of ventriculitis.

On April 17 a large collection of cerebrospinal fluid was tapped from the front of the temporal lobe at a depth of 6 cm. ; 55 c.cm. was allowed to escape. This contained 80 mg. of protein per 100 c.cm. and 15 cells per c.mm. : globulin was not increased.

Subsequent lumbar punctures in May showed variable results, the cerebrospinal fluid being one day opalescent, one day clear. The pressure, however, remained consistently high, varying from 250 mm. to 400 mm.

At this stage the patient came under my care. The white blood cell count was 12,500 per c.mm. of blood. He was still having systemic chemotherapy, plus daily intrathecal penicillin. On May 9 an intracerebral abscess was tapped in the left temporal lobe, 30 c.cm. of pus being removed. This abscess was drained by tubes. The pus proved to be sterile.

On May 13 the brain was tapped again, and a second intracerebral abscess entered behind the first. The pus was at first thin and watery but later became thick and mucoid ; 50 c.cm. was aspirated. Examination of this pus revealed no organisms. Protozoa were looked for in a wet smear, and large mononuclear cells were seen which resembled precystic forms of amœbæ but were not mobile.

A full subtemporal decompression was performed on the same day, the bone flap being removed. A specimen of pus was sent warm for immediate examination, and *numerous vegetative amœbæ, actively mobile*, were seen in the first slide. Some of these contained red blood cells, some only inclusion bodies. They were identified by the pathologist as *Entamœba histolytica.*

The patient was put on a course of emetine gr. 1 daily for ten days. A brisk reaction followed the exhibition of this drug. The decompression began to swell. On May 18 a further 70 c.cm. of pus was aspirated from the two abscesses. At that time it was noted that the amount of pressure in each abscess could be assessed roughly according to the nature of the dysphasia—whether it was predominantly motor or predominantly sensory. Even towards the end of the illness the patient did not completely lose the power of the right leg, arm, or face. Although drowsy when his intra-cerebral pressure was high, he became much less so as soon as pressure was relieved, and then he could still understand simple commands and utter a few simple words.

Each cavity was gently irrigated with 0·2 per cent. emetine hydrochloride solution in sterile water, and 10,000 units of penicillin and 1 c.cm. of thorotrast were left in the abscess. Thorotrast is reported to have no deleterious effect on the potency of penicillin (Pennybacker, 1945).

On May 20 it was noted that the patient had a Horner's syndrome on the left side, with a small pupil and redness of the left face and conjunctiva. During the next few days every site which had ever produced pus, except that next to the falx, produced yellow or "anchovy sauce" type of purulent discharge.

A culture taken on May 23 produced a growth of alarming significance—a non-hæmolytic streptococcus which was penicillin-resistant. The second prolonged course of penicillin was stopped and he was given streptomycin both intramuscularly and intrathecally (10,000 units). On May 30 a second course of eight emetine injections was begun. On June 2 he showed a left palatal palsy, hoarseness, and difficulty in swallowing. Next day the white blood cell count revealed a disturbing drop to 3,400 per c.mm. of blood (polymorphs 55 per cent.). All sulphonamides were therefore stopped and were not given again. A week later the white blood cells had risen steadily to 12,300 per c.mm. (polymorphs 72 per cent.), and three days after that the white blood cells were 23,600 per c.mm. with 81 per cent. of polymorphs. His decompression continued to enlarge.

Since the situation was desperate, a desperate remedy was tried, and the whole abscess area in the left temporal region was marsupialized. Through this cerebral fungus there extruded at various times six firm encapsulated abscesses. Alternate courses of streptomycin and penicillin were continued. Neck retraction became very marked. On June 29 it was obvious that the fungus communicated with the ventricle. The lumbar spinal fluid pressure, which had been at 180–200, fell to below 100 mm. Next day he died.

Necropsy.—The brain showed a widespread meningo-encephalitis with the left hemisphere riddled with abscesses of varying sizes. Round these cavities was a firm grey or pink tissue resembling granulation tissue. The space between the spinal cord and the dura at the foramen magnum was filled by a firm felt of grey granulation tissue, forming a thick tube round the cord. This tissue extended over the front of the pons and midbrain and up to the pituitary region.

The only visible abnormalities elsewhere in the body were abscesses of the lower lobe of the right lung, with thickened pleura over the right base.

Histological sections were reported on by Major L. Krainer, R.A.M.C. :

Section of abscess wall (of the brain) showed the lumen of the abscess to be full of pus. The pus cells were degenerating polymorphonuclear leucocytes. The wall

of the abscess showed softening and granulation, with thrombosing capillaries. Gram stain revealed groups of cocci in chains in the pus. There were mononuclear cells with foamy protoplasm, some of which contained red blood corpuscles. Heidenhain stain shows that these were Gitter cells. There was no evidence of amœbæ in the section examined.

Sections of the spleen showed reticulum cell hyperplasia of the pulp. There were central fatty change of the lobules of the liver. The tubular epithelium of the kidney was granular, and the tubules distended. No abnormality was detected in the pancreas. A section of the lung showed bronchitis, bronchiolitis, peri-bronchitis, and an area of old unresolved pneumonia with small abscesses containing polymorphonuclears. Gram stain showed scanty gram-positive cocci, single, in pairs, clumps, and short chains in the affected areas.

Central Nervous System.—There was an encapsulated abscess the size of an orange in the base of the left frontal lobe, and a collapsed abscess cavity in the left parieto-temporal region corresponding to the area of operation which communicated with the left lateral ventricle. The ventricles contained thick, greenish pus, and there was severe basal meningitis.

Histological examination of four sections from the abscesses and from the basal meninges showed suppurative inflammation with numerous polymorphonuclear cells. Nucleated and degenerated Gitter cells were seen in fair numbers. Some of the degenerated Gitter cells showed shadows of nuclei, but these were not of the type seen in the vegetative amœba.

Diagnosis.—There was histological and circumstantial evidence that the cerebral abscesses were secondary to unresolved pneumonia with abscess formation in the lung. (From the clinical point of view it is of interest that septic spots appeared in the skin at the onset of the cerebral condition. No amœbæ were seen in the material examined.)

Discussion

In view of the treatment with emetine totalling 18 grains, it is not surprising that no amœbæ were found in the brain abscesses at necropsy. The comparative absence of blockage of cerebrospinal fluid circulation in spite of long-standing basal meningitis is noteworthy. It seems probable that the streptococcus found on March 1 had been present from the beginning along with the amœbæ. What would section of one of the skin papules have revealed?

The absence of a history of diarrhœa or of bowel lesions at necropsy is worthy of comment, and there it seems likely that the lung abscess played a part in the pathological picture from an early stage.

Prolonged discussion of a single case affords little profit, but the following points are worthy of note.

1. Whenever a brain abscess is tapped in a part of the world where entamœba histolytica is endemic, the fresh pus should be examined for protozoa.

2. Even in an early case treatment should include (*a*) radical surgical intervention, (*b*) emetine, and (*c*) anti-pyogenic chemotherapy.

The week following the exhibition of emetine should be one of constant observation and readiness to drain and decompress as circumstances indicate. At the same time infection from a secondary pyogenic invader should be treated as a meningo-encephalitis of the most virulent kind, and should be dealt with on the lines suggested for pneumococcal, streptococcal, or staphylococcal meningitis following aural sepsis (Smith, Duthie, and Cairns, 1946; Smith, Schiller, and Cairns, 1946). It is probably unwise to use emetine locally in the treatment of the abscesses, in view of the brisk reaction which followed in this case.

Summary

A case of amœbic abscesses in the brain is described. The cerebral illness lasted four and a half months and ended fatally. Treatment with sulphonamides, penicillin, streptomycin, and emetine was given but the emetine was administered for the first time three months after the illness began. Agranulocytosis necessitated cessation of the sulphonamide therapy after fourteen weeks.

The unusually long period of survival in this case suggests that if modern chemotherapy is given early a cure may be obtainable; the lines along which early treatment might be directed are outlined.

Thanks are due to Capt. N. M. Nair, I.A.M.C., and Major L. Krainer, R.A.M.C., who were responsible for the pathological reports on the smears and later on the sections. I am indebted also to Lt.-Col. A. J. Slessor, Major R. H. Hannah, Capt. W. J. Connolly, and Capt. O. M. Brewster, R.A.M.C., from whose comprehensive notes it has been possible to determine the early history. With particular pleasure, acknowledgment is made to Major W. J. Woodhouse, I.A.M.C., Specialist Radiologist, but for whose suggestion the original examination for amœbæ would not have been made.

I am also indebted to Colonel E. Percival, R.A.M.C., for permission to forward this case for publication.

References

Pennybacker, J. (1945). *Proc. roy. Soc. Med.*, **38**, 431.
Smith, H. V., Duthie, E. S., and Cairns, H. (1946). *Lancet*, **1**, 185.
——, Schiller, F., and Cairns, H. (1946). *Proc. roy. Soc. Med.*, **39**, 613.
Stein, A., and Kazan, A. (1942). *J. Neuropath. exp. Neurol.*, **1**, 32.

BOOK REVIEWS

THE PSYCHOLOGY OF BEHAVIOUR DISORDERS

Norman Cameron

(New York : Houghton Mifflin and Company. 1947. Pp. 622+xxi. Price 25s.)

Fashion in psychopathology comes and goes rather rapidly ; it was not long ago that analytical attention was primarily directed towards studying individual reactions to a stock selection of infantile traumatic situations. Now, with the current trend towards sociological interpretation, certain analysts are looking away from the patient, in fact ignoring him altogether and evaluating the symptom complex he presents in terms of environmental influences. Carried to extremes this discipline regards the social pattern as a matrix of equivalent units each differing only in the history of its experience. It is from near this extreme position that Professor Cameron has reinterpreted psychiatry.

The first part of his book is devoted to a statement of the sociological forces which form one major cause of emotional stress. The development of the individual in relation to his environment is described in detail, and such controversial issues as infantile sexuality, oral and anal eroticism, are woven sensibly into a coherent picture of learning and maturation. The rest, the major part, is a description of the classical psychiatric syndromes. The symptomatology of each is accurately described, and they are re-evaluated in terms of biosocial psychopathology.

The author unfortunately dismisses without adequate explanation a large body of accepted knowledge in the fields both of psychology and psychiatry. He denies any constitutional basis for personality differences, and ignores the existing evidence for hereditary factors in the ætiology of schizophrenia and the cyclical insanities. Empirical modern therapy is dismissed. It is brusquely, if correctly, characterized as " cerebral assault." The result is a lengthy but very one-sided book of considerable naiveté. As a good illustration of the latter point, it is noted that the fanciful Freudian dichotomy of a conscious and an unconscious mental life is dismissed, but in the next sentence the author himself divides mental processes into those that are " reportable " and those that are " unreportable."

As an introduction to the sociopathology of everyday life this book is of interest and value, but as a reasoned re-evaluation of the ætiology of behaviour disorders it is biased and misleading.

WAR, POLITICS, AND INSANITY

C. S. Bluemel

(Denver, Colorado. The World Press, Inc. 1948. Pp. 117. Price $2.)

This book is deceptive in its dust cover—red, white, black, and flashy ; but under this is a quiet blue board with discreet lettering. The style is simple, almost *too* simple, a little ingenuous for one with degrees and the title of psychiatrist, and it is difficult to avoid a sense of disappointment that the author did not go deeper into some of the interesting problems he touches.

The thought and style are clear, as can be judged from such remarks as, " In the legend of democracy it is a postulate that the majority is always right. Manifestly the principle is faulty, for opinion may be wrong even when it is unanimous "—obvious perhaps, but often forgotten—or again, " Despite the beauty of the thought (i.e., that the majority is always right), it is impossible to distill wisdom from mass opinion."

When Dr. Bluemel discusses obsessive, compulsive, and aggressive behaviour, both the inadequacy of language to express complex ideas and the inability of present-day psychological thinking to discriminate between different moving forces and intentions becomes evident. It is true to say that a man who is always worrying about his own teeth and staring at other people's has an obsession, and equally true to say that Columbus was obsessed with the idea of a new world in the west. Nevertheless the two obsessions are different in kind ; the potential results are different from the beginning, and the motive forces, could we see them, must surely also be different. The compulsion of Florence Nightingale to look after the sick is very different in quality from the compulsion of Carry Nation to smash up public houses. But present-day psychology has not found an instrument by which to measure these differences ; until it does so it will see only the outer skin, as it were, of behaviour. Certainly to discuss such different kinds of " obsession " in one breath—as this author does—implies a faulty approach.

The chapters " Democracy in Action " and " An Appraisal of Democracy " are interesting reading because the inherent rightness and workability of democracy are too often taken for granted in spite of the opposite views of many of the greatest philosophers, and in spite of the fact that a wholly democratic state has never existed. It would be interesting to have an analysis of the philosophic implications of the democratic idea and psychological assessment of achievements of approximately democratic governments.

In the last chapter, " The Future of Democracy," the author puts forward a scheme for limiting the franchise and governmental responsibility to the academically and morally qualified. " When the world is governed by normal men it will cease to be the arena of the battle captains and men will live together in peace." Yes, indeed. But what is " normal " ? And how is the danger to be overcome that abnormal or subnormal people will impose their own standards, calling them " normal " ? Where, in fact, are " normal " men to be found ?

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Myanesin is indicated for the production of relaxation of the abdominal muscles during anæsthesia; its use eliminates the risk of respiratory collapse and the need for deep anæsthesia. Details of dosage and other relevant information on request.

MEDICAL DEPARTMENT
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